



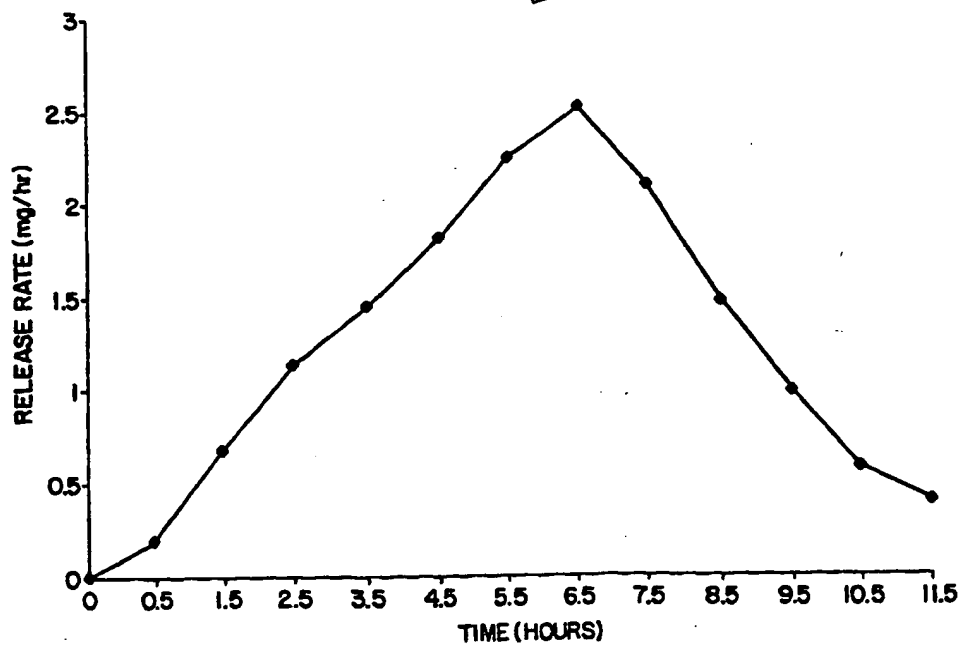
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(21) International Application Number: PCT/US97/22016 (22) International Filing Date: 12 November 1997 (12.11.97)  (30) Priority Data: 60/031,741 25 November 1996 (25.11.96) US 08/967,606 10 November 1997 (10.11.97) US  (71) Applicant: ALZA CORPORATION [US/US]; 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US).  (72) Inventors: HAMEL, Lawrence, G.; 1215 Arbor Court, Mountain View, CA 94040 (US). AYER, Atul, Devdatt; 931 Bautista Court, Palo Alto, CA 94303 (US). WRIGHT, Jeri, D.; 11305 Rolling Hills Drive, Dublin, CA 94568 (US). LAM, Andrew; 1506 38th Avenue, San Francisco, CA 94122 (US). SHIVANAND, Padmaja; 870 E. El Camino Real #44, Mountain View, CA 94040 (US).  (74) Agents: SABATINE, Paul, L. et al.; Alza Corporation, 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US).			(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.                  Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>

(54) Title: ASCENDING-DOSE DOSAGE FORM



(57) Abstract

A dosage form and a method are disclosed for delivering to a human patient a drug in an ascending amount over time.

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1                                    ASCENDING-DOSE DOSAGE FORM

2  
3                                    FIELD OF THE INVENTION

4  
5                    This invention relates to a dosage form for delivering an increasing  
6 dose of drug. The invention concerns further a dosage form for delivering  
7 an increasing dose of drug per unit time over an extended time for continuous  
8 effective therapy. The invention pertains additionally to a novel longitudinal  
9 dosage form comprising a lengthwise dimension greater than its diameter-  
10 wise dimension for delivering an increased dose of drug over a sustained  
11 period of therapy. The invention concerns further a method for delivering a  
12 dose of drug from the dosage form provided by this invention in an ascending  
13 dose for a known therapeutic purpose.

14  
15                                   BACKGROUND OF THE INVENTION

16  
17                    For a long time, from antiquity to the present, pharmacy and  
18 medicine in all societies used medicines as chemotherapeutics, cancer  
19 chemotherapeutics, antiviral therapeutics, for treating neurological maladies,  
20 as immunosuppressive drugs, for pain relief, for managing mood, thought,  
21 feeling, behavior, psychological personality and pharmacological benefits.  
22 The medicines used in these therapies are represented by analgesics,  
23 antineoplastics, cytoprotectives, vasomodifiers, opioids, barbiturates,  
24 hypnotics, central nervous system stimulants, psychostimulants,  
25 psychodepressants, alcohols, cannabinoids, catecholamines, and therapies  
26 known in the United States Pharmacopeia, 1997 Ed. While these medicines  
27 or therapies have a benefit, a serious problem, called tolerance, is associated  
28 with their use. The development of tolerance to a drug results from adaptive  
29 changes within the affected patient, such that the therapeutic response is  
30 reduced in the presence of the same dose of drug. Tolerance to some drugs,  
31 for example, to opioids, is characterized by a shortened duration and  
32 decreased intensity of the therapeutic effect. Most of the tolerance seen with

1 many drugs is due to adaptation of cells in the nervous system to the drug's in  
2 vivo action, as noted in The Pharmacological Basis of Therapeutics,  
3 Goodman and Gilman, 7th Ed., p. 534 (1940).

4 In the broad practice of medicine to which this invention is relevant,  
5 one class of these drugs that has become the standard intervention for the  
6 management of behavior and personality, including attention deficit disorders,  
7 is the central nervous system stimulants. While this invention presents the  
8 central nervous system acting drugs in detail, it is understood the invention is  
9 generic and it embraces drugs broadly as administered by the dosage form,  
10 and the mode and the manner of this invention.

11 The benefits perceived by health-care providers, physicians,  
12 psychiatrists, psychologists, social workers, and clinicians are dramatic for  
13 central nervous system drugs, and this has resulted in the widespread and  
14 accepted use of the central nervous system acting drugs to treat attention  
15 deficit disorder. In the latest period for collecting data, 1996, it was observed  
16 that about two percent of the school-aged female population and about six  
17 percent of the school-aged male population, for a total of about two million  
18 patients, were administered medication for attention deficit disorder.

19 Prior to this invention, drugs including opioids, barbiturates, hypnotics,  
20 central nervous system stimulants, central nervous system depressants,  
21 psychostimulants, alcohols, cannabinoids, catecholamines and other drugs  
22 were administered by a standard pharmaceutical dosage form. For example,  
23 one prior art dosage form for administering a drug consists in using an  
24 immediate release tablet containing the drug. This immediate release form  
25 delivers the drug by instant dumping of the drug and produces uneven blood  
26 levels characterized by peaks and valleys. For an immediate-release dosage  
27 form containing a drug that has a rapid onset and a short half-life, this drug  
28 may need multiple doses each day and this can result in swings in blood  
29 levels as the medication loses its therapeutic effect. This type of dosage  
30 form does not provide the needed therapy over an extended time.

1 Another prior art dosage form for dispensing a drug is the sustained-  
2 release dosage form. The sustained-release dosage form delivers a drug in  
3 a nonascending profile, often in a descending profile, over time. This dosage  
4 form, however, may not provide the required therapy and the appropriate  
5 blood pattern. For drugs, such as the central nervous system acting drugs,  
6 that are delivered from a sustained-release, nonascending dosage form,  
7 the patient often develops an acute tolerance to the drug which is manifested  
8 by a short duration and a decrease in the intensity needed for acceptable  
9 therapy. The prior art sustained-release dosage form is devoid of means  
10 that compensate for its shortcomings inherent therein.

11 The above presentation teaches that a critical and pressing need  
12 exists for a novel dosage form for delivering a drug that overcomes the  
13 shortcomings known to the prior art. That is, a long-felt need exists for a  
14 dosage form for (1) delivering a drug in a sustained-ascending rate that  
15 simultaneously reduces or eliminates the need for frequency of daily dosing;  
16 for (2) delivering a drug in a sustained-compensating dose to substantially  
17 compensate for acute tolerance to the drug and thereby maintain a  
18 preselected clinical profile; for (3) administering the drug in an increasing  
19 dose to lessen or eliminate acute or chronic tolerance to the drug to provide  
20 effective therapy; and (4) for delivering the drug in a sustained, ascending-  
21 controlled profile clinically indicated for both medical and psychomedical  
22 effects.

#### 23 24 OBJECTS OF THE INVENTION 25

26 Accordingly, in view of the above presentation, it is an immediate  
27 object of this invention to provide a novel and unique dosage form that  
28 overcomes the shortcomings known to the prior art and thereby makes an  
29 advancement in the drug dispensing art.

1 Another object of the invention is to make available to the medical  
2 and mental health arts a novel and unique dosage form that provides an  
3 ascending dose of drug over a sustained time.

4 Another object of the invention is to provide a dosage form for  
5 maintaining the therapeutic effect of a drug in a patient that acquires a  
6 tolerance to the drug, wherein the dosage form comprises a dose of drug  
7 that is released in an ascending dose to a patient that acquired tolerance  
8 to the drug to lessen the effect of tolerance and concomitantly provide the  
9 intended therapy.

10 Another object of the invention is to provide a dosage form for  
11 maintaining the therapeutic effect of a drug in a patient that acquired acute  
12 tolerance to the drug, wherein the dosage form is designed and shaped as a  
13 tablet for oral administration and delivers to a patient the drug in a dosage  
14 form controlled, increasing dose to compensate for the acute tolerance  
15 associated with this drug.

16 Another object of the invention is to provide a dosage form designed  
17 and shaped as an osmotic tablet for oral administration into the  
18 gastrointestinal tract, comprising a dose of drug for administering to a patient  
19 that acquires chronic tolerance to the drug, for administering the drug in a  
20 controlled increasing dose, to provide drug compensation for the acquired  
21 chronic tolerance associated with the drug.

22 Another object of the invention is to make available a dosage form  
23 comprising a length greater than its thickness for lessening the incidence of  
24 acquired tolerance in a patient, wherein the dosage form is characterized by  
25 administering the drug in a sustained and increasing dose over time to  
26 produce the intended therapeutic effect.

27 Another object of the invention is to provide a dosage form  
28 manufactured as a longitudinal tablet possessing a lengthwise dimension in  
29 excess of its diameter-wise dimension for administering a drug selected from  
30 the group consisting of an opioid, barbiturate, hypnotic, central nervous  
31 system stimulant, central nervous system depressant, psychostimulant,



1   cannabinoid and catecholamine in a controlled, changing dose that  
2   overcomes the shortcomings known to the prior art.

3           Another object of the invention is to make available a method for  
4   lessening the incidence of acquired tolerance in a patient administered a  
5   drug that develops tolerance in the patient, wherein the method comprises  
6   an improvement by administering a dosage form manufactured initially as a  
7   compressed tablet that in operation in a fluid environment dispenses a drug  
8   in a sustained and increasing dose to substantially lessen the unwanted  
9   effects of tolerance and to produce the intended therapy over four hours to  
10  thirty hours.

11          Another object of the invention is to make available a dosage form,  
12  designed as an oral pharmaceutically acceptable tablet, comprising a first  
13  layer of drug and a second layer that pushes the first layer from the tablet,  
14  to provide a sustained and ascending dose of drug.

15          Another object of the present invention is to make available a method  
16  for administering a drug in a sustained and increasing dose by administering  
17  an osmotic dosage tablet comprising a drug composition that delivers the  
18  drug in an initial concentration, followed by a second, higher concentration  
19  from the original drug composition to effect a sustained and ascending dose  
20  of drug.

21          Another object of the invention is to make available a dosage form  
22  manufactured as an osmotic tablet comprising a single composition  
23  containing a drug administered in a sustained and ascending dose profile  
24  over time.

25          Another object of the invention is to make available a dosage form  
26  manufactured as an osmotic tablet comprising an immediate-release dose of  
27  drug on the exterior of the osmotic tablet, and a prolonged-ascending dose in  
28  the interior of the osmotic tablet, which exterior and interior doses operate  
29  successively to provide an ascending dose of drug to negate acquired and  
30  developed tolerance.

1 Another object of this invention is to make available a dosage form  
2 manufactured as an osmotic oral tablet comprising an immediate dose of drug  
3 on the exterior of the osmotic tablet, and an interior bilaminate comprising a  
4 drug laminate comprising a dose of drug, and an expandable laminate  
5 comprising an expandable hydrogel, which osmotic tablet in operation  
6 delivers a dose of drug immediately in up to one hour from the exterior of  
7 the osmotic tablet, and a dose of drug in from fifteen minutes up to twenty-  
8 four hours from the interior of the osmotic tablet by the expandable laminate  
9 pushing the interior drug from the osmotic tablet, whereby through the  
10 combined operations of the exterior dose, the interior laminate, and the  
11 expandable laminate, the osmotic tablet provides an ascending dose of  
12 drug for therapy over time.

13 These objects, as well as other objects, features and advantages of  
14 this invention will become more apparent from the following detailed  
15 disclosure of the invention accompanied by the accompanying claims.

#### 16 17 BRIEF DESCRIPTION OF THE DRAWING FIGURES

18  
19 Figure 1 illustrates an ascending release rate profile for a dosage  
20 form comprising the drug pseudoephedrine hydrochloride as provided by  
21 the invention;

22 Figure 2 depicts an ascending-increasing dose release rate for a  
23 dosage form of the invention comprising the central nervous system  
24 stimulating drug methylphenidate hydrochloride; and,

25 Figure 3, depicts the release rate in mg/hr for methylphenidate from a  
26 dosage form provided by the invention.

#### 27 28 DETAILED DESCRIPTION OF SPECIFICATION

29  
30 In accordance with the practice of this invention, it has now been  
31 discovered a novel dosage form can be made available characterized by an

1 ascending rate of drug delivery over time. The dosage form provided by this  
2 invention delivers a drug at a continuously increasing rate for a predetermined  
3 period of time. The dosage form of this invention is unexpected and it is a  
4 breakaway from the prior art existing dosage form technologies that deliver  
5 a drug at a constant zero-order unchanging rate over time. The dosage form  
6 of this invention avoids delivery at a zero order rate as it delivers a drug  
7 continuously in an ascending rate over time. The profile of the prior art  
8 dosage form consists of a short start-up in delivery, followed by a constant  
9 unchanged rate. The profile of this invention departs from the prior art by  
10 making available a dosage form wherein the drug release rate follows an  
11 ascending profile to achieve a desired drug delivery pattern. The dosage  
12 form of this invention achieves the ascending pattern by combining the  
13 dimensions of the dosage form with the internal formulation of the dosage  
14 form.

15 The dosage form of this invention comprises a wall that surrounds  
16 an internal compartment. The wall of the dosage form comprises a  
17 semipermeable composition permeable to the passage of fluid present in  
18 an environment of use, such as the aqueous biological fluid of the  
19 gastrointestinal tract, and the wall is impermeable to the passage of drug.  
20 The wall maintains its physical and chemical integrity during the drug  
21 dispensing life of the dosage form. The semipermeable wall comprises a  
22 polymer selected from the poly(cellulose) group consisting of cellulose  
23 acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose  
24 diacetate and cellulose triacetate. The wall comprises 100 wt% (weight  
25 percent) of said poly(cellulosic) polymer possessing a number-average  
26 molecular weight of 15,000 to 4,000,000. The wall, in another manufacture,  
27 can comprise from 40 wt% to 100 wt% of the poly(cellulosic) polymer and  
28 from 0 to 35 wt% of a hydroxypropylalkylcellulose selected from the group  
29 consisting of hydroxypropylmethylcellulose, hydroxypropylethylcellulose,  
30 hydroxypropylbutylcellulose, and hydroxypropylpentylcellulose of 9,000 to  
31 240,000 number-average molecular weight; 0 to 25 wt% of a

1 hydroxyalkylcellulose comprising a member selected from the group  
2 consisting of hydroxymethylcellulose, hydroxyethylcellulose,  
3 hydroxypropylcellulose, and hydroxybutylcellulose of 7,500 to 200,000  
4 number-average molecular weight; and 0 to 25 wt% of poly(ethylene glycol)  
5 of 190 to 40,000 intrinsic viscosity molecular weight. The total weight of all  
6 components comprising the wall is equal to 100 wt%. Wall-forming polymers  
7 are known in U.S. Patent Nos. 3,845,770; 3,916,899; 4,036,228; 4,111,202;  
8 and 5,178,866.

9 The dosage form comprises one or more than one exit in the wall that  
10 connects the exterior of the dosage form with the interior of the dosage form.  
11 The term "exit" as used herein comprises a passageway, orifice, pore,  
12 micropore, micro-opening, hollow fiber, capillary tube, porous overlay, porous  
13 insert, and osmotic opening for dispensing a drug from the dosage form.  
14 The exit passageway embraces further a material that erodes, or is leached  
15 from the wall in a fluid environment of use, such as the gastrointestinal tract.  
16 Representative materials for forming an erodible passageway include erodible  
17 poly(glycolic) acid, erodible poly(lactic acid), erodible poly(orthoester),  
18 erodible poly(orthocarbonate), erodible poly(acetal), a gelatinous filament,  
19 poly(vinyl alcohol), leachable materials including fluid removable pore-forming  
20 polysaccharides, salts, sugars and oxides. An exit can be formed by leaching  
21 compounds such as sorbitol, lactose or glucose. The exit can have any  
22 operative shape such as round, triangular, square, or elliptical. The dosage  
23 form can be provided with one or more passageways close together or in  
24 spaced apart positions on a common surface of the dosage form.  
25 Passageways and equipment for forming an exit are disclosed in U.S.  
26 Patent Nos. 3,845,770; 3,916,899; 4,063,064; 4,088,864; 4,200,098;  
27 4,285,987; and 5,178,866.

28 The dosage form comprises internally a first drug layer and a second  
29 expandable layer. The first layer is next to the exit to provide for drug delivery  
30 from the dosage form. The first layer comprises a dose of 240 ng  
31 (nanograms) to 700 mg (milligrams) of drug, and from 1 mg to 200 mg of a

1 pharmaceutically acceptable carrier. The pharmaceutically acceptable carrier  
2 comprises a hydrophilic polymer selected from the group consisting of a  
3 poly(alkylene oxide) of 25,000 to 1,000,000 number-average molecular  
4 weight where a 5% aqueous solution exhibits a viscosity at 25°C of 12 to  
5 17,600 cps (centipoise) represented by a member selected from the group  
6 consisting of poly(methylene oxide), poly(ethylene oxide), poly(propylene  
7 oxide), poly(butylene oxide), copolymer poly(ethylene oxide)-poly(propylene  
8 oxide); and a blend of two different poly(alkylene oxides), such as a  
9 poly(alkylene oxide) of 40,000 to 500,000 molecular weight with a different  
10 poly(alkylene oxide) of 40,000 to 500,000 molecular weight, a poly(ethylene  
11 oxide) of 100,000 molecular weight with a poly(ethylene oxide) of 200,000  
12 molecular weight, or a poly(ethylene oxide) of 200,000 molecular weight with  
13 a poly(ethylene oxide) of 300,000 molecular weight, which poly(alkylene  
14 oxide) polymers are available from Union Carbide Corp.; 0 mg to 200 mg  
15 of a pharmaceutical excipient such as starch, talc, mannitol, sorbitol, glucose,  
16 fructose, polysaccharides or silicon dioxide; 0 mg to 125 mg of a hydrophilic  
17 pharmaceutically acceptable carboxyvinylpolymer, also known as  
18 carboxypolyalkylene polymer, possessing a 7,500 to 1,000,000 number-  
19 average molecular weight, including a carboxyvinylpolymer of 450,000  
20 number-average molecular weight, a carboxyvinylpolymer of 750,000  
21 number-average molecular weight, a carboxyvinylpolymer of 1,250,000  
22 number-average molecular weight, and a carboxyvinylpolymer of  
23 3,000,000 number-average molecular weight, as disclosed in U.S.  
24 Patent Nos. 2,798,053; 2,909,462; and 3,825,068, and available as  
25 Carbopol® polymer from B.F. Goodrich Company; and 0 mg to 250 mg  
26 of a pharmaceutically acceptable alkali carboxyalkylcellulose, wherein the  
27 alkali is sodium or potassium represented by sodium carboxymethylcellulose  
28 of 10,000 to 7,000,000 viscosity-average number molecular weight, available  
29 from the Hercules Corporation; a surfactant selected from 0.0 mg to 7.5 mg  
30 of a member selected from the group consisting of amphoteric, anionic,  
31 cationic, and nonionic surfactants, as represented by sorbitan trioleate,

1 sorbitan tristearate, ethylene glycol fatty acid ester, polyethylene glycol  
2 monostearate, sorbitan sesquioleate, glycerol monostearate, sorbitan  
3 monooleate, propylene glycol monolaurate, sorbitan monostearate, diethylene  
4 glycol monolaurate, sorbitan monopalmitate, polyoxyethylene mannitol  
5 dioleate, sorbitan monolaurate, polyoxyethylene lauryl ether, polyoxyethylene  
6 monostearate, polyethylene glycol 400 monostearate, triethanolamine oleate,  
7 polyoxyethylene alkyl phenol, polyethylene alkyl aryl ether, polyoxyethylene  
8 sorbitan monolaurate, polyoxyethylene sorbitan monostearate,  
9 polyoxyethylene sorbitan monooleate, polyoxyethylene sorbitan  
10 monopalmitate, polyoxyethylene monostearate, polyoxyethylene sorbitan  
11 monolaurate, polyoxyethylene lauryl ether, sodium oleate, and sodium  
12 lauryl sulfate, which surfactants are known in Pharmaceutical Sciences,  
13 Remington, 17th Ed., pp. 1305-1306 (1985); 0 mg to 20 mg of a  
14 hydroxypropylalkylcellulose binder selected from the group consisting  
15 of hydroxypropylmethylcellulose, hydroxypropylethylcellulose,  
16 hydroxypropylbutylcellulose and hydroxypropylpentylcellulose of 9,000  
17 to 750,000 number-average molecular weight, available from the Dow  
18 Chemical Company, and a polyvinylpyrrolidone binder of 7,500 to 350,000  
19 molecular weight; and 0.0 mg to 20 mg of a hydroxyalkylcellulose selected  
20 from the group consisting of hydroxymethylcellulose, hydroxyethylcellulose,  
21 hydroxypropylcellulose, hydroxybutylcellulose and hydroxypentylcellulose of  
22 7,500 to 750,000 weight-average molecular weight, available from Aqualon  
23 Company; and 0.01 mg to 5 mg of a lubricant such as stearic acid,  
24 magnesium stearate, calcium stearate, potassium oleate, magnesium  
25 laureate and calcium palmitate. The expression "pharmaceutically  
26 acceptable" as used herein means the polymer, compound or drug denotes  
27 nontoxic and is acceptable for oral administration to a human patient.

28 The dosage form comprises a second layer that displaces or pushes  
29 the first drug layer through the exit port from the dosage form. The second  
30 layer comprises 100 ng to 400 mg of a hydrophilic osmopolymer selected  
31 from the group consisting of a poly(alkylene oxide) of 1,500,000 to

1 10,000,000 number-average molecular weight; or an alkali  
2 carboxyalkylcellulose of 1,750,000 to 10,000,000 of viscosity-average  
3 number molecular weight; 0 to 100 mg of a hydroxypropylalkylcellulose  
4 comprising hydroxypropylmethylcellulose, hydroxypropylethylcellulose,  
5 hydroxypropylbutylcellulose and hydroxypropylpentylcellulose of 9,000 to  
6 750,000 number-average molecular weight; 0 to 400 mg, generally 25 mg  
7 to 400 mg, of a hydroxyalkylcellulose selected from hydroxymethylcellulose,  
8 hydroxyethylcellulose, hydroxypropylcellulose and hydroxybutylcellulose of  
9 7,500 to 1,500,000 number-average molecular weight; from 0 to 250 mg,  
10 with a present manufacture of 10 mg to 175 mg, of an osmagent, also known  
11 as osmotically effective solute, osmotically effective compound, and osmotic  
12 agent, including inorganic and organic compounds, selected from the group  
13 consisting of magnesium sulfate, magnesium chloride, sodium chloride,  
14 lithium chloride, potassium sulfate, sodium sulfate, lithium sulfate, potassium  
15 chloride, sodium sulfate, magnesium succinate, tartaric acid; carbohydrates  
16 such as raffinose, sucrose, glucose and lactose; from 0.001 mg to 10 mg of a  
17 surfactant selected from the group consisting of amphoteric, anionic, cationic  
18 and nonionic surfactants, present in the first drug layer; 0 mg to 20 mg of a  
19 carboxyvinylpolymer of 7,500 to 10,000 number-average molecular weight,  
20 present in the first drug layer; 0 mg to 5 mg of a colorant compound to identify  
21 the dosage form, such as red ferric oxide or black ferric oxide; and 0 mg to  
22 5 mg of a lubricant including the lubricants presented in the first drug layer.

23 The dosage form provided by this invention is designed and shaped  
24 as a dosage form tablet. The dosage form tablet comprises a length greater  
25 than its width individually. The dosage form tablet comprises a length of  
26 5 mm to 28 mm, and a width of 2.50 mm to 10 mm. The dosage form tablet  
27 provided by this invention comprises in the second layer 60% to 95% of  
28 osmopolymer, or 60% to 95% of a combination comprising an osmopolymer  
29 and an osmagent. The high percent of osmopolymer, or high percent  
30 osmopolymer and osmagent composition, joined with the dimensions of the

1 dosage form tablet, enables the dosage form tablet to make available an  
2 ascending delivery of drug for 2 hours to 24 hours.

3 Representative of a drug present in the drug layer comprises a drug  
4 composition comprising an opioid, barbiturate, hypnotic, central nervous  
5 system acting drug, psychostimulant, psychodepressant, analgesic, alcohol,  
6 cannabinoid, and catecholamine. Examples of drugs are central nervous  
7 system acting drugs for the management of attention deficit disorder,  
8 including catecholamines and drugs that can mimic their action. The drugs  
9 for this therapy comprise a member selected from the group consisting of  
10 amphetamine, dextroamphetamine, methamphetamine, methylphenidate,  
11 racemic methylphenidate, threomethylphenidate, ethylphenidate,  
12 phenylisopropylamine and pemoline. The drugs include racemates,  
13 stereoisomers and enantiomers of a racemic drug. The drugs include their  
14 pharmaceutically acceptable salts, such as a member selected from the  
15 group consisting of hydrochloride, fumarate, sulfate, phosphate, lactate,  
16 malate, acetate, tartrate, hydrobromide, citrate, pamoate, maleate, ascorbate,  
17 gluconate, aspartate, and salicylate.

18 The invention comprises further, on the external surface of the dosage  
19 form, a coat composition comprising a drug. The coat composition is an  
20 external overcoat carried by the dosage form. The external overcoat on the  
21 wall of the dosage form comprises a dose of drug, and the overcoat  
22 cooperates with the interior compartment comprising a dose of drug that  
23 delivers the drug, to provide an initial unexpected ascending drug delivery  
24 profile. The overcoat provides an initial dose of drug followed by a dose of  
25 drug from the interior of the dosage form to give an ascending drug delivery  
26 profile. The overcoat comprises 10 ng to 100 mg of a drug that is delivered in  
27 up to one hour, followed by the dose from the dosage form. The dose of drug  
28 from the interior is delivered over 24 hours. The overcoat comprises a drug  
29 selected from the group consisting of opioids, barbiturates, hypnotics,  
30 psychostimulants, psychodepressants, central nervous system acting drugs,  
31 analgesics and catecholamines. Representative of individual drugs present in



1 the overcoat comprise a drug selected from the group consisting of  
2 amphetamine, dextroamphetamine, methamphetamine, methylphenidate,  
3 racemic methylphenidate, threomethylphenidate, ethylphenidate,  
4 alkylphenidate, phenylisopropylamine, and pemoline. These drugs include  
5 their pharmaceutically acceptable salts such as a member selected from the  
6 group consisting of hydrochloride, sulfate, phosphate, acetate, hydrobromide,  
7 pamoate, malate, maleate, fumarate, ascorbate, tartrate and citrate.  
8 Representative of a drug embodiment present in the overcoat is an  
9 alkylphenidate comprising 10 ng to 25 mg of methylphenidate.

10 The overcoat comprises the drug blended with a pharmaceutically  
11 acceptable carrier. The pharmaceutically acceptable carrier comprises an  
12 aqueous, drug-releasing carrier selected from the group consisting of an  
13 alkylcellulose, methylcellulose, ethylcellulose, hydroxyalkylcellulose,  
14 hydroxymethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose,  
15 hydroxybutylcellulose, hydroxypropylalkylcellulose,  
16 hydroxypropylmethylcellulose, hydroxypropylethylcellulose,  
17 hydroxypropylbutylcellulose, methyl dextrose, acacia, guar gum,  
18 pregelatinized starch, propylene glycol alginate and cyclodextrin.

19 The overcoat comprises 0.01 wt% to 15 wt% of the pharmaceutically  
20 acceptable carrier. The dosage form overcoat in another manufacture  
21 comprises 0.01 wt% to 5 wt% of a member selected from the group  
22 consisting of polyethylene glycol, polypropylene glycol, polyvinylpyrrolidone,  
23 and acetylated triglycerides. The overcoat provides needed drug therapy,  
24 for example, methylphenidate, as the overcoat dissolves or undergoes  
25 dissolution in the presence of fluid present in the gastrointestinal tract of a  
26 patient. Thus, the overcoat provides drug therapy on oral administration into  
27 the patient's drug receiving environment, the gastrointestinal tract, for an  
28 immediate therapeutic benefit.

29 The wall of the dosage form in one manufacture is formed by an air-  
30 suspension procedure. This procedure consists of suspending and tumbling  
31 compressed bilayer cores in a current of air and wall-forming composition until

1 a wall is applied forming and surrounding an internal compartment containing  
2 the bilayer core. The air-suspension procedure is well suited for forming the  
3 wall. The air-suspension procedure is described in U.S. Patent Nos.  
4 2,799,241 and 5,082,668. The wall can be formed in an air-suspension  
5 coater using cosolvents. Representative cosolvents are: methylene  
6 dichloride-methanol, 80:20 wt:wt; or acetone-water cosolvent 85:15, or 90:10,  
7 or 95:5, or 99:1 wt:wt, using 1% to 7% solids. Other wall-forming techniques  
8 can be used, such as a pan coating system, or a wall forming composition  
9 deposited by successive spraying of the composition accompanied by  
10 tumbling in a rotating pan. A pan coater may be used to produce thicker  
11 walls. A large volume of solvent can be used in a solvent system to produce  
12 a thinner wall. Finally, the wall-coated compartment is dried in an oven at  
13 30°C to 50°C for up to a week, or in a humidity controlled oven at 50 RH  
14 (relative humidity) and 50°C for 18 hours to 3 days.

15 The first and second layers of the invention are made by standard  
16 manufacturing techniques. For example, in one manufacture the drug and  
17 other ingredients are blended and pressed into a solid layer. The drug and  
18 the ingredients can be blended with a solvent and mixed into a semisolid or  
19 solid formed by conventional methods such as ball-milling, calendering,  
20 stirring or roller milling, and then pressed into a preselected shape. The first  
21 layer possesses dimensions that correspond to the internal dimensions of the  
22 area the layer occupies in the dosage form. It also possesses dimensions  
23 corresponding to the second layer for forming a contacting bilayer  
24 arrangement therewith. The push layer comprising the osmopolymer, or  
25 osmopolymer and osmagent, is placed in contact with the first drug layer.  
26 The push layer, a displacement layer for displacing the drug layer from the  
27 dosage form, is manufactured using the techniques for providing the first drug  
28 layer. The layering of the first drug layer and the second displacement layer  
29 can be fabricated by conventional press layering techniques. The bilayered  
30 compartment-forming core is surrounded and coated with an outer wall  
31 comprising a semipermeable composition. An exit is laser drilled through the

1 wall to contact the first drug layer. The dosage form is optically oriented  
2 automatically by the laser equipment for forming the exit passageway.

3 In another manufacture, the dosage form is manufactured by the wet  
4 granulation technique. In the wet granulation technique, for example, the  
5 drug and the ingredients comprising a drug layer are blended using an  
6 organic solvent, such as isopropyl alcohol-methylene dichloride 80:20 v:v  
7 (volume:volume), or methanol-methylene dichloride, as the granulation fluid.  
8 Other granulating fluid, such as denatured alcohol 100%, can be used for this  
9 purpose. The ingredients forming the drug layer are individually passed  
10 through a screen and then thoroughly blended in a mixer. Next, other  
11 ingredients comprising the drug layer are dissolved in a portion of the  
12 granulation fluid, such as the solvents described above. Then, the latter  
13 prepared wet blend is slowly added to the drug blend with continual mixing in  
14 the blender. The granulating fluid is added until a wet blend is produced,  
15 which wet mass is forced through a screen onto oven trays. The blend is  
16 dried for 7 to 24 hours at 30°C to 50°C. The dry granules are then sized with  
17 a screen. Next, a lubricant is passed through a screen and added to the dry  
18 screen granule blend. The granulation is put into milling jars and mixed on a  
19 jar mill for 1 to 15 minutes. The other drug layer and the displacement layers  
20 are made by the same wet granulation techniques. The compositions are  
21 pressed into their individual layers in standard presses, such as a layer press.

22 Another manufacturing process that can be used for providing the  
23 compartment-forming compositional layers comprises blending the powdered  
24 ingredients for each layer independently in a fluid bed granulator. After the  
25 powdered ingredients are dry blended in the granulator, a granulating fluid,  
26 for example, poly(vinylpyrrolidone) in water, or in denatured alcohol, or in  
27 95:5 ethyl alcohol/water, or blends of ethanol and water, is sprayed onto the  
28 powders. Optionally, the ingredients can be dissolved or suspended in the  
29 granulating fluid. The coated powders are then dried in a granulator. This  
30 process granulates all the ingredients present therein while adding the  
31 granulating fluid. After the granules are dried, a lubricant, such as stearic

1 acid, calcium stearate, magnesium oleate, potassium oleate, or magnesium  
2 stearate, is added to the granulator. The granules for each separate layer  
3 are then pressed in the manner described above.

4 The dosage form of this invention is manufactured in another  
5 manufacture by first mixing a known dose of drug with compositional layer-  
6 forming ingredients, and then pressing under one-eighth to three tons the  
7 composition into a solid layer possessing dimensions that correspond to the  
8 internal dimensions of the compartment of the dosage form. The contacting  
9 second layer, comprising an osmopolymer, or an osmopolymer and an  
10 osmagent, is manufactured in a like manner. In another manufacture, the first  
11 and second layers independently are manufactured by mixing the drug and  
12 composition forming ingredients and a solvent into a solid, or into a semisolid,  
13 by conventional methods such as ball milling, calendering, stirring or roller  
14 milling, and pressed into a layer. Next, the first layer is placed next to a layer  
15 of a displacement composition comprising an osmopolymer and an optional  
16 osmagent. Then, the two-layered core is surrounded with a semipermeable  
17 wall. The layering of the first layer and the second layer can be accomplished  
18 by layer tablet press technique and longitudinal compressed tablet technique.  
19 A wall can be applied by molding, spraying or dipping the pressed-shape  
20 bilayered core into wall forming materials. Another technique that can be  
21 used for applying the wall is the air-suspension coating procedure. This  
22 procedure consists in suspending and tumbling the two-layered laminate  
23 in a current of air until the wall forming composition surrounds the bilayer.  
24 The air-suspension procedure is described in U.S. Patent No. 2,799,241;  
25 J. Am. Pharm. Assoc., Vol. 48, pp. 451-459 (1979); and ibid., Vol. 49,  
26 pp. 83-84 (1960). Other manufacturing procedures are described in  
27 Modern Plastic Encyclopedia, Vol. 46, pp. 62-70 (1969); and in  
28 Pharmaceutical Sciences, Remington, 14th Ed., pp. 1626-1979 (1970),  
29 published by Mack Publishing Co., Easton, PA.

30 Exemplary solvents suitable for manufacturing the wall, the layer and  
31 the wall include inert inorganic and organic solvents. The solvents broadly

1 include members selected from the group consisting of aqueous solvents,  
2 alcohols, ketones, esters, ethers, aliphatic hydrocarbons, halogenated  
3 solvents, cycloaliphatics, aromatics, heterocyclic solvents and mixtures  
4 thereof. Typical solvents include acetone, diacetone alcohol, methanol,  
5 ethanol, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl acetate,  
6 isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methyl propyl  
7 ketone, n-hexane, n-heptane ethylene glycol monoethyl ether, ethylene  
8 glycol monoethyl acetate, methylene dichloride, ethylene dichloride,  
9 propylene dichloride, carbon tetrachloride, chloroform, nitroethane,  
10 nitropropane, tetrachloroethane, ethyl ether, isopropyl ether, cyclohexane,  
11 cyclooctane, benzene, toluene, naphtha, tetrahydrofuran, diglyme, aqueous  
12 and nonaqueous mixtures thereof, such as acetone and water, acetone and  
13 methanol, acetone and ethyl alcohol, methylene dichloride and methanol,  
14 ethylene dichloride and methanol, and methylene dichloride and ethanol.  
15 The solvents are disclosed in U.S. Patent No. 5,030,456.

16

17

#### DETAILED DESCRIPTION OF THE EXAMPLES

18

19 The following examples are illustrative of the present invention, and the  
20 examples should not be considered as limiting the scope of the invention in  
21 any way, as these examples, and other equivalents thereof, will become  
22 apparent to those versed in the art in the light of the present disclosure and  
23 the accompanying claims.

24

25

#### EXAMPLE 1

26

27 An osmotic dosage form designed and shaped to deliver a drug that  
28 stimulates the central nervous system by administering a drug in an  
29 ascending release profile is manufactured as follows: First, a binder solution  
30 is prepared as follows: 300 g of poly(vinylpyrrolidone) having a number-  
31 average molecular weight of 40,000 is added to a mixing vessel containing

1 2700 g of distilled water. The mixture is stirred until the poly(vinylpyrrolidone)  
2 dissolves in the water and produces a clear solution. Next, a drug formulation  
3 is prepared as follows: 6,564 g of poly(ethylene oxide) having a number-  
4 average molecular weight of 200,000 is passed through a 40 mesh screen.  
5 Then, 3,282 g of the screened poly(ethylene oxide) is placed into the bowl of  
6 a fluid bed granulator. Next, 1,024 g of central nervous system acting  
7 methylphenidate hydrochloride is placed into the granulator with the  
8 poly(ethylene oxide). Then, 100 g poly(vinylpyrrolidone) of number-average  
9 molecular weight 40,000 is added to the granulator; then the remaining  
10 3,182 g of poly(ethylene oxide) is added to the granulator. The addition of  
11 the dry ingredients into the bowl is performed so that the methylphenidate  
12 hydrochloride is located between two layers of poly(ethylene oxide). The  
13 granulation is started with the ingredients inside the bowl fluidized for  
14 2 minutes to obtain a uniform mixing of the powders. Next, the binder  
15 solution is sprayed onto the powder bed through nozzles at a spray rate of  
16 100 g/min. During the spraying process, the airflow is maintained at 500 cfm  
17 and the temperature kept at 25°C. During the spraying operation, the solution  
18 is sprayed for 30 seconds, followed by a shaking time of 10 seconds during  
19 which time the powders adhering to the filterbags are dislodged into the  
20 granulating chamber. At the end of the spraying operation, the granules are  
21 dried in the granulating chamber for an additional 5 to 10 minutes to obtain  
22 dry granulation. The methylphenidate hydrochloride granules are passed  
23 through a fluid air mill with a 7 mesh screen for size reduction. The screen  
24 is U.S. Sieve Series as disclosed in Chemical Engineer's Handbook, Perry,  
25 6th Ed., pp. 21-15 (1984). Next, the screened granules are placed in a  
26 blender to which 8 g of magnesium stearate (screened through a 40 mesh  
27 screen) and 4 g of powdered butylated hydroxy toluene (screened through a  
28 60 mesh screen) is added to the granules and mixed together.

29 Next, the displacement or push composition is prepared as follows:  
30 First a binder solution is prepared by adding 937.5 g of poly(vinylpyrrolidone)  
31 of 40,000 number-average molecular weight to 8437.5 g of distilled water.

1 This mixture is stirred until the poly(vinylpyrrolidone) dissolves in water to  
2 yield a clear solution. Next, displacement osmotic granules are prepared as  
3 follows: First, 13452.5 g of poly(ethylene oxide) having a number-average  
4 molecular weight of 7,000,000 is placed into the bowl of a fluid bed  
5 granulator. Next, 312.5 g of poly(vinylpyrrolidone) of 40,000 number-average  
6 molecular weight is added to the bowl. Then, 10,000 g of osmagent sodium  
7 chloride and 250 g of red ferric oxide, which have been milled using a  
8 21 mesh screen, are placed into the bowl. The bowl is attached to the main  
9 body of the granulator and the granulation is initiated. Initially, the powder  
10 bed inside the bowl is fluidized for 3 minutes to obtain uniform mixing of the  
11 powders. Then, the binder solution is sprayed onto the powder bed and the  
12 binder solution sprayed thereon at a rate of 240 g/min. During the spraying,  
13 the air flow is maintained at 1000 cfm and the temperature kept at 25°C.  
14 The solution is sprayed for 30 seconds, followed by shaking for 10 seconds,  
15 during which time the powders adhering to the filterbags can be dislodged  
16 into the granulating chamber. At the end of the spraying operation, the  
17 granules are dried in the granulating chamber for an additional 10 to 15  
18 minutes to obtain dry granulation. The granules are then passed through  
19 an air mill with a 7 mesh screen for size reduction. The granules are then  
20 transferred to a blender, and 25 g of magnesium stearate (screened through  
21 a 40 mesh screen) and 12.5 g of butylated hydroxy toluene (screened  
22 through a 60 mesh screen) are added to the granules and mixed together.

23 Next, the drug composition comprising the methylphenidate and the  
24 displacement osmotic composition are compressed together using an  
25 automated tablet compression machine capable of compressing the two  
26 layers longitudinally together. First, 110 mg of the methylphenidate  
27 composition forming layer is added to the die cavity of 4.7 mm diameter,  
28 tamped, and then 132 mg of the displacement osmotic composition is placed  
29 into the die and compressed together using 0.2 metric tons of pressure.

1           Next, a wall-forming composition comprising 90% cellulose acetate  
2   having an acetyl content of 39.8%, and 10% poly(ethylene glycol) having  
3   an average molecular weight of 3350 is formed around the bilayered core.  
4   The semipermeable composition is dissolved in a mixture of acetone and  
5   water (90:10 wt:wt) to provide solid composition of the solution at 5%.  
6   The compressed bilayered cores are placed into a 61 cm coating pan and  
7   the coating solution sprayed onto the cores at a spray rate of 100 ml/min.  
8   The temperature is kept at 35°C during the coating process.

9           Next, one 30 mil (0.76 mm) orifice is drilled through the semipermeable  
10   wall connecting the drug composition with the exterior of the dosage form.  
11   The residual solvent is removed by drying at 45°C and 45% relative humidity  
12   in an oven for 48 hours. At the end of the drying cycle, the humidity is turned  
13   off, and the dosage forms are dried at 45°C for an additional 4 hours.

14           The dosage form prepared according to this example comprises a first  
15   drug layer comprising 110 mg consisting of 14.08 mg of methylphenidate,  
16   90.26 mg of poly(ethylene oxide) of 200,000 number-average molecular  
17   weight, 5.5 mg of poly(vinylpyrrolidone) of 40,000 number-average molecular  
18   weight, 0.11 mg of magnesium stearate, and 0.055 mg of butylated hydroxy  
19   toluene. The dosage form displacement layer 2 comprises 132 mg  
20   composed of 71.032 mg of poly(ethylene oxide) of 7,000,000 number-  
21   average molecular weight, 52.8 mg of osmagent sodium chloride, 6.6 mg of  
22   poly(vinylpyrrolidone) of 40,000 number-average molecular weight, 1.32 mg  
23   of red ferric oxide, 0.132 mg of magnesium stearate, and 0.066 mg of  
24   butylated hydroxy toluene. The semipermeable wall weighed 17 mg and  
25   comprised 15.3 mg of cellulose acetate consisting of 39.8% acetyl content,  
26   and 1.7 mg of poly(ethylene glycol) of 3350 number-average molecular  
27   weight. The dosage form possessed a 30 mil (0.76 mm) orifice.

28           The dosage form delivered methylphenidate in an ascending release  
29   rate. The dosage from delivered 0.22 mg in the first hour, 1.45 mg in the  
30   second hour, 1.72 mg in the third hour, 1.84 mg in the fourth hour, 2.05 mg in  
31   the fifth hour, 2.21 mg in the sixth hour, 2.13 mg in the seventh hour, 1.26 mg



1 in the eighth hour, 0.39 mg in the ninth hour, and 0.09 mg in the tenth hour,  
2 with a residual of 0.72 mg in the dosage form.

3

4

#### EXAMPLE 2

5

6 The procedure of Example 1 is followed with the processing steps as  
7 previously described, except the drug in this example is a member selected  
8 from the group consisting of pemoline, deanol, deanol acetamidobenzoate,  
9 benzphetamine hydrochloride, deanol aceglumate, clortermine,  
10 diethylpropion, fenfluramine, dextroamphetamine phosphate, and  
11 dextroamphetamine sulfate.

12

13

#### EXAMPLE 3

14

15 An osmotic dosage form adapted, designed and shaped as an  
16 oral tablet for delivering a drug with an ascending release profile is  
17 manufactured as follows: First, a composition is prepared by passing  
18 through a 40 mesh screen 393.85 g of poly(ethylene oxide) having a  
19 molecular weight of about 300,000. Then 63.65 g of drug selected from  
20 the group consisting of amphetamine sulfate, difluanine hydrochloride,  
21 flubanilate, mefexamide, methamphetamine, pseudoephedrine and  
22 pyrovalerone hydrochloride; 15.00 g of polyoxyl 40 stearate; and 25.00 g  
23 of hydroxypropylmethylcellulose having a number-average molecular weight  
24 of 11,200 are screened to 40 mesh and then added to the poly(ethylene  
25 oxide). The four ingredients are mixed for about 10 minutes in a conventional  
26 mixer. Then 50 ml of denatured, anhydrous ethanol is slowly added to the  
27 mixer and the mixing continued for an additional 10 minutes. The wet  
28 granulation is passed through a 20 mesh screen, dried at room temperature  
29 for 16 hours, and passed again through a 20 mesh screen. Finally, 2.5 g of  
30 magnesium stearate is added to the granulation and all the ingredients mixed  
31 for an additional 3 minutes.

1           Next, a second displacement composition is prepared by mixing  
2   267.5 g of poly(ethylene oxide) having a number-average molecular weight of  
3   7,000,000 with 175 g (35%) of osmagent sodium chloride; 25 g of Carbomer®  
4   934, a carboxyvinyl polymer possessing a 3,000,000 number-average  
5   molecular weight, disclosed in U.S. Patent Nos. 3,074,852, 3,634,584, and  
6   4,248,847, commercially available from BF Goodrich Chemicals, Cleveland,  
7   OH; and 5 g of red iron oxide. The homogenous blend is passed through a  
8   40 mesh screen, and 25 g of hydroxypropylmethylcellulose having a number-  
9   average molecular weight of 11,200 is added to all the ingredients. The  
10   ingredients are blended in a conventional planetary mixer for 10 minutes.  
11   Then, 50 ml of denatured, anhydrous ethanol is slowly added to the blending  
12   mixture and all the ingredients mixed for an additional 5 minutes. The freshly  
13   prepared wet granulation is passed through a 20 mesh screen, allowed to dry  
14   at room temperature for 16 hours, and again passed through a 20 mesh  
15   screen. The screened granulation is mixed with 2.5 g of magnesium stearate  
16   for 3 minutes.

17           A laminating press is used to form the bilaminate. First, 110 mg of  
18   the first drug composition is added to a 4.7 mm die cavity and tamped. Then,  
19   115 mg of the second expandable composition is added to the die cavity, and  
20   the two separate compositions pressed into a bilaminated core under 1/2 ton  
21   of pressure.

22           Next, the bilaminated core is surrounded with a semipermeable wall.  
23   The wall-forming composition comprises 95% cellulose acetate having an  
24   acetyl content of 39.8%, and 5% polyethylene glycol having a molecular  
25   weight of 3350. The wall forming composition is dissolved in acetone:water  
26   (90:10 wt:wt) solvent to make a 5% solids solution. Then, 22 mg of the wall  
27   forming composition is sprayed onto and around this bilaminate in a Hi-Coater  
28   pan coater. Then, a 30 mil (0.76 mm) exit orifice is drilled by laser or  
29   mechanical drill in the center of the drug laminate side of the osmotic device.  
30   The residual solvent is removed by drying for 48 hours at 50°C and 50%  
31   relative humidity, followed by one hour drying at 50°C.

1 A dosage form prepared by this example comprises a 110 mg drug  
2 layer comprising 12.73 wt% pseudoephedrine hydrochloride, 78.77 wt%  
3 poly(ethylene oxide) of 300,000 number-average molecular weight, 5 wt%  
4 hydroxypropylmethylcellulose of 11,200 number-average molecular weight,  
5 3 wt% polyoxyl 40 stearate and 0.5 wt% magnesium stearate. The 115 mg  
6 displacement layer comprises 53.5 wt% poly(ethylene oxide) possessing a  
7 7,000,000 number-average molecular weight, 5 wt%  
8 hydroxypropylmethylcellulose possessing 11,200 number-average  
9 molecular weight, 35 wt% sodium chloride, 0.5 wt% magnesium stearate,  
10 5 wt% Carbopol® carboxyvinylpolymer, and 1 wt% red ferric oxide. The  
11 semipermeable wall comprises 20.9 mg of cellulose acetate of 39.8% acetyl  
12 content and 1.1 mg of poly(ethylene glycol) of 4,000 number-average  
13 molecular weight. The dosage form comprises a 30 mil orifice (0.76 mm)  
14 and exhibits the ascending release rate profile seen in accompanying  
15 Figure 1.

#### 17 EXAMPLE 4

18  
19 A dosage form designed and adapted as a tablet for the oral  
20 administration of methylphenidate pharmaceutically acceptable salt in an  
21 ascending release profile is manufactured as follows: First, 163.4 g of  
22 poly(ethylene oxide) having an average molecular weight of 200,000 is  
23 passed through a 40 mesh screen and placed into the bowl of a conventional  
24 planetary mixer. Next, 25.6 g of methylphenidate hydrochloride is weighed  
25 and placed into the bowl containing the poly(ethylene oxide). Next, 10 g of  
26 hydroxypropylmethylcellulose possessing a 11,200 molecular weight is  
27 passed through a 40 mesh screen and placed into the bowl containing the  
28 poly(ethylene oxide) and methylphenidate hydrochloride. Next, 0.5 g of  
29 FD&C Blue Dye No. 1 is placed into the bowl of the mixer. The four  
30 ingredients are blended together in the planetary mixer for 10 minutes.  
31 Next, 100 ml of denatured anhydrous ethanol is gradually added to the

1 mixer with continued mixing for 10 minutes to change the consistency of the  
2 dry powder to that of granules. The wet granulation is then passed through  
3 a 20 mesh screen, dried at room temperature for 16 hours, and then passed  
4 through a 20 mesh screen. Next, 0.5 g of magnesium stearate, which has  
5 been passed through a 40 mesh screen, is added to the granulation, and all  
6 the ingredients are mixed for an additional 1 minute.

7       Next, a displacement layer is manufactured as follows: First, 107 g of  
8 poly(ethylene oxide) having an average molecular weight of 7,000,000, 80 g  
9 of sodium chloride (40%), 10 g of hydroxypropylmethylcellulose (USP grade)  
10 possessing a 11,200 molecular weight, and 2 g of red ferric oxide are passed  
11 through a 40 mesh screen and then placed into the bowl of a conventional  
12 planetary mixer. The powder mixture is then blended together until a  
13 homogenous blend is formed. Next, 50 ml of denatured anhydrous ethanol is  
14 added to the mixer with continued mixing over a period of 5 to 10 minutes,  
15 such that the consistency of the dry powder changes to granules. The wet  
16 granulation is passed through a 20 mesh screen, dried at room temperature  
17 for 16 hours, and then passed through a 20 mesh screen. Next, 1 g of  
18 magnesium stearate which has been passed through a 40 mesh screen is  
19 added to the granulation, and all the ingredients are mixed for an additional  
20 1 minute.

21       Next, a bilayer press is used to compress the two layers together to  
22 form a tablet dosage form. First, 110 mg of the drug composition is added to  
23 the 4.7 mm die cavity and lightly tamped. Next, 115 mg of the displacement  
24 composition is weighed and placed into the die cavity, and the two layers are  
25 compressed together using 1/2 ton of pressure to form a bilayer pretablet.

26       A wall for enveloping the bilayer pretablet to yield the finished tablet is  
27 formed as follows: First, a semipermeable composition composed of 90%  
28 cellulose acetate (having an acetyl content of 39.8%) and 10% polyethylene  
29 glycol having an average molecular weight of 3350 is prepared by dissolving  
30 in a mixture of acetone and water (the solvents are mixed together in a ratio  
31 of 90:10 wt:wt), such that the solids composition of the solution is 5%. The

1 bilayer tablets are placed in a coater pan, and 20 mg of the semipermeable  
2 composition is sprayed on to the bilayer tablets. Next, a 30 mil (0.76 mm)  
3 orifice is drilled on the drug layer side of the bilayer tablet using an automatic  
4 tableting positioning laser drill. Next, the semipermeable coated tablets are  
5 dried for 48 hours at 50°C and 50% relative humidity to remove the residual  
6 solvents. The release rate ascending profile for a dosage form prepared  
7 according to the example is seen in accompanying Figure 2. Drawing  
8 Figure 2 depicts the release of methylphenidate hydrochloride from a  
9 semipermeable, longitudinal dosage form.

#### 11 EXAMPLE 5

12  
13 The procedure of the above examples is followed, with the further  
14 embodiment that a drug overcoat and an optional taste-masking coat is  
15 overcoated onto the exterior surface of the wall. The overcoat, in one  
16 manufacture, comprises 60 wt% of hydroxypropylmethylcellulose of  
17 9,200 number-average molecular weight and 40 wt% methylphenidate  
18 hydrochloride. The hydroxypropylmethylcellulose is added to water  
19 and mixed until a uniform solution results. Then, the methylphenidate  
20 hydrochloride is added to the solution and mixed such that a clear  
21 solution results. The final solution has a solid composition of 10%.  
22 Next, semipermeable walled dosage forms are placed in a coater and 10 mg  
23 of the drug overcoat is sprayed onto the semipermeable wall that surrounds  
24 the internal bilayer compressed tablet. Then, overcoated dosage forms are  
25 dried for 10 minutes at 40°C. For taste masking, a suspension of Opadry®,  
26 a powder blend comprised of hydroxypropylmethylcellulose, titanium dioxide,  
27 polyethylene glycol and polysorbate 80, is prepared in water to effect a solid  
28 content of 10%. The drug overcoated dosage forms are placed in a coater  
29 and 9 mg of the taste-masking solution is sprayed over the drug overcoat to  
30 produce a double-overcoated dosage form. Next, the dosage forms are dried  
31 at 40°C for 10 to 12 minutes to yield the operable dosage forms.

EXAMPLE 6

The procedures set forth in the above examples are followed, with the manufactures as described above, except in this invention, a first dosage form is provided wherein the drug layer comprises 28 mg of methylphenidate hydrochloride, and a second dosage form is provided wherein the drug layer comprises 42 mg of methylphenidate hydrochloride.

EXAMPLE 7

The procedures set forth in the above examples are followed with the manufacturing conditions set forth as previously indicated, except that in this example a dosage form is provided wherein the second displacement layer comprises 65 mg of sodium carboxymethylcellulose osmopolymer of 3,500,000 number-average molecular weight and an osmagent combination comprising 58 mg of dextrose-fructose in equal proportions; and a dosage form wherein the second displacement layer comprises 72 mg of poly(ethylene oxide)-poly(propylene oxide) copolymer of 7,900,000 number-average molecular weight and 47.8 mg of co-osmagent sodium chloride-dextrose (23.9 mg - 23.9 mg).

EXAMPLE 8

A dosage form designed and adapted to deliver a drug in an ascending release rate profile is manufactured according to this example.

First, a first layer-forming composition comprising a dose of drug is manufactured as follows: 157.8 mg of poly(ethylene oxide) having a number-average molecular weight of 200,000 is passed through a 40 mesh screen (U.S. Sieve) and placed into the bowl of a conventional planetary mixer. Next, 31.2 g of the drug methylamphetamine hydrochloride is added to the

1 mixer. Then, 10 g of hydroxypropylmethylcellulose of 16,000 number-  
2 average molecular weight is passed through a 40 mesh screen and added  
3 to the mixer comprising the methylamphetamine hydrochloride and the  
4 poly(ethylene oxide). Then, 0.5 g of FD&C Blue Dye No. 1, for color  
5 identification, is added to the bowl of the mixer. The ingredients are blended  
6 in the mixer for 10 minutes to produce a homogenous composition. Next,  
7 100 ml of denatured anhydrous ethanol is added gradually to the mixer, with  
8 continual mixing over a period of 5 to 10 minutes to change the consistency of  
9 the dry ingredients to wet granules. The wet granulation is passed through a  
10 20 mesh screen, dried at room temperature for 16 hours, and then passed  
11 through a 20 mesh screen. Then, 0.5 g of magnesium palmitate is passed  
12 through a 40 mesh screen, added to the homogenous composition, and all  
13 the ingredients mixed for an additional minute.

14 Next, a displacement layer, the second layer, is prepared as follows:  
15 First, 53 g of poly(ethylene oxide) of 7,500,000 number-average molecular  
16 weight, 54 g of poly(propylene oxide) of 5,000,000 number-average  
17 molecular weight, 80 g of osmagent sodium chloride, 10 g of  
18 hydroxypropylethylcellulose of 24,000 number-average molecular  
19 weight, and 2 g of red ferric oxide are passed through a 40 mesh screen  
20 and then placed into the bowl of a mixer. The ingredients are blended  
21 together to form a homogenous blend. Next, 50 ml of denatured anhydrous  
22 ethanol is added to the mixer, accompanied by continual mixing for  
23 10 minutes to produce wet granules. The wet granules are passed through  
24 a 20 mesh screen, dried at room temperature for 16 hours, and then passed  
25 through a 20 mesh screen. Next, 1 g of stearic acid lubricant is passed  
26 through a 40 mesh screen, added to the granulation, and all the ingredients  
27 mixed for an additional minute.

28 Next, the first drug layer-forming composition and the second  
29 displacement layer-forming composition are pressed together into contacting  
30 layers as follows: First, 33 mg of the first composition is added to a 0.55 cm  
31 die cavity and tamped lightly. Then, 57 mg of the displacement composition

1 is added to the die and tamped lightly, to provide two layers that are  
2 compressed using 1/2 ton of pressure to form a bilayer tablet.

3 Next, the bilayer is surrounded with a semipermeable wall as follows:

4 First, a semipermeable wall forming composition is prepared comprising  
5 95% cellulose having an acetyl content of 39.8%, and 5% polyethylene glycol  
6 of 3350 number-average molecular weight (available from Union Carbide Co.)  
7 by dissolving the ingredients in a mixture of acetone and water in a 90:10  
8 (v:v) ratio to provide solid composition at 5%. The bilayer tablets are placed  
9 in a pan coater and 15 mg of the semipermeable wall forming composition is  
10 sprayed onto the bilayer tablet. Next, a 30 mil (0.76 mm) orifice is drilled on  
11 the drug side to connect the first layer with the outside of the dosage form.  
12 The dosage form tablets are dried at 50°C and 50% relative humidity to  
13 remove the residual solvents. The dosage form comprises 5.2 mg of  
14 methamphetamine hydrochloride to give an extended ascending release  
15 tablet. Additional dosage forms are provided according to the invention  
16 comprising 10 mg and 15 mg methamphetamine hydrochloride extended  
17 ascending release tablet.

18

#### 19 EXAMPLE 9

20

21 The above examples are followed to provide a dosage form comprising  
22 an external coat of a pharmaceutically acceptable drug and an internal  
23 composition comprising a pharmaceutically acceptable drug, which dosage  
24 form when in operation in a fluid biological environment delivers the external  
25 overcoat drug in 0 to 1 hour, and delivers the internal drug in the amounts of  
26 15% in 0 to 2 hours, 30% in 2 to 4 hours, 33% in 4 to 6 hours, 18% in 6 to  
27 8 hours, and 4% in 8 to 10 hours.



EXAMPLE 10

The above examples are followed to provide a dosage form comprising an external overcoat comprising 100 ng to 100 mg of drug and an internal composition comprising 10 ng to 500 mg of drug, which dosage form when in operation in the fluid environment of the gastrointestinal tract delivers the 100 ng to 100 mg external overcoat in 0 to 1 hour, and delivers the internal 10 ng to 500 mg in an increasing release of 20% in 0 to 4 hours, 30% in 4 to 8 hours, 40% in 8 to 12 hours and 10% in 12 to 16 hours, to substantially overcome tolerance to delivered drug.

EXAMPLE 11

An osmotic dosage form designed and shaped to deliver methylphenidate hydrochloride to a patient in need of methylphenidate therapy in an ascending release profile is manufactured as follows:

Composition of drug layer 1: The following procedure is used to manufacture 8,000 g of layer 1 composition:

A. Preparation of binder solution.

260 g of hydroxypropylmethylcellulose having average molecular weight of 11,200 is added to a mixing vessel containing 3250 g of water. This mixture is stirred until the hydroxypropylmethylcellulose dissolves in water and a clear solution is formed. This solution is referred to as the binder solution.

B. Preparation of methylphenidate hydrochloride granules.

4380 g of polyethylene oxide having an average molecular weight of 200,000 is passed through a 40 mesh screen. Then, 2190 g of the screened poly(ethylene oxide) is placed into the bowl of a fluid bed granulator. Next, 2032 g of sorbitol is added to the powder bed, followed by 1024 g of methylphenidate hydrochloride into the bowl over the poly(ethylene oxide). Next, 140 g of hydroxypropylmethylcellulose is added

1 to the bowl. The remaining 2190 g of poly(ethylene oxide) is then added to  
2 the bowl. The addition of dry ingredients into the bowl is performed so that  
3 the methylphenidate hydrochloride is located in between the two layers of  
4 poly(ethylene oxide). The bowl is attached to the main body of the granulator  
5 and the granulation process is initiated. Initially, the powder bed inside the  
6 bowl is fluidized for 2 minutes to obtain uniform mixing of the powders. Next,  
7 the binder solution is sprayed onto the powder bed through nozzles such that  
8 the solution is sprayed at a rate of 60 g/min. During the spraying process,  
9 the process air flow is maintained at 500 cfm and the product temperature is  
10 maintained at 22°C. During the spraying operation, the solution is sprayed for  
11 30 seconds followed by a shaking time of 10 seconds, during which time the  
12 powders adhering to the filterbags may be dislodged into the granulating  
13 chamber. At the end of the spraying operation, the granules are dried in the  
14 granulating chamber for an additional 5 to 10 minutes to obtain dry  
15 granulation. The methylphenidate hydrochloride granules are then passed  
16 through a fluid air mill with a 7 mesh screen for size reduction. The size-  
17 reduced granules are then placed into a suitable blender. 160 g of  
18 magnesium stearate (screened through a 40 mesh screen) and 4 g of  
19 powdered butylated hydroxy toluene (screened through a 60 mesh screen)  
20 are added to the granules and mixed together.

21 Composition of layer 2: The following procedure is used to manufacture  
22 8,000 g of displacement layer 2 composition:

23 A. Preparation of binder solution.

24 260 g of hydroxypropylmethylcellulose having an average molecular  
25 weight of 11,200 is added to a mixing vessel containing 3250 g of water.  
26 This mixture is stirred until the hydroxypropylmethylcellulose dissolves in  
27 water and a clear solution is formed. This solution is referred to as the binder  
28 solution.

29 B. Preparation of osmotic layer granules.

30 4308 g of poly(ethylene oxide) having an average molecular weight of  
31 7,000,000 is placed into the bowl of a fluid bed granulator. Next, 140 g of

1 hydroxypropylmethylcellulose having an average molecular weight of 11,200  
2 is added to the bowl. Then, 3,200 g of sodium chloride and 80 g of red ferric  
3 oxide, which have been screened using a 21 mesh screen, are then placed  
4 into the bowl. The bowl is attached to the main body of the granulator and  
5 the granulation process is then initiated. Initially, the powder bed inside the  
6 bowl is fluidized for 3 minutes to obtain uniform mixing of the powders. Next,  
7 the binder solution is sprayed onto the powder bed through nozzles, such that  
8 the solution is sprayed at a rate of 80 g/min. During the spraying process, the  
9 process air flow is maintained at 400 cfm, and the product temperature is  
10 maintained at 22°C. During the spraying operation, the solution is sprayed for  
11 30 seconds followed by a shaking time of 10 seconds, during which time the  
12 powders adhering to the filterbags may be dislodged into the granulating  
13 chamber. At the end of the spraying operation, the granules are dried in the  
14 granulating chamber for an additional 10 to 15 minutes to obtain dry  
15 granulation. The process parameters may be adjusted to obtain a quality  
16 product. The granules then are passed through a fluid air mill with a 7 mesh  
17 screen for size reduction. The size-reduced granules are then placed into a  
18 suitable blender. Next, 8 g of magnesium stearate (screened through a  
19 40 mesh screen) and 4 g of powdered butylated hydroxy toluene (screened  
20 through a 60 mesh screen) are added to the granules and mixed together.

21 C. Compression of the layers. —

22 The methylphenidate granules-forming layer and the osmotic granules-  
23 forming layer are compressed together using an automated tablet  
24 compression machine capable of compressing the two layers together  
25 longitudinally. First, 110 mg of methylphenidate granules (layer 1) is added  
26 into the die cavity of a 3/16" diameter modified ball tooling, tamped, and then  
27 132 mg of the osmotic layer granulation (layer 2) is placed into the die and  
28 compressed together using 0.2 metric tons of pressure.

29 D. Application of semipermeable membrane wall.

30 The semipermeable membrane wall is composed of 47.5% cellulose  
31 acetate (having an acetyl content of 39.8), 47.5% cellulose acetate (having an

1 acetyl content of 32.0), and 5% polyethylene glycol having an average  
2 molecular weight of 3350. The semipermeable membrane-forming  
3 composition is dissolved in a mixture of methylene chloride and methanol  
4 (the solvents are mixed together in a ratio of 80:20 wt:wt), such that the solids  
5 composition of the solution is 4%. The compressed systems are placed into a  
6 61 cm coating pan and the coating solution is sprayed onto the tablets such  
7 that the solution is sprayed at a rate of 100 ml/min/gun. The product  
8 temperature is maintained at 25°C; the coating process is stopped when the  
9 semipermeable membrane composition has been sprayed onto the  
10 compressed systems.

11 Next, one 30 mil (0.76) orifice is drilled, using a mechanical drill bit or a  
12 laser, on the drug layer side of the coated systems. The residual solvents  
13 remaining after the coating are removed by drying the systems at 45°C and  
14 45% relative humidity in an oven for 48 hours. At the end of this drying cycle,  
15 the humidity is turned off, and the systems are dried at 45°C for an additional  
16 4 hours to complete the drying process.

17 A methylphenidate dosage form assembled as described contains  
18 110 mg of drug containing layer 1, which is composed of 12.8%  
19 methylphenidate hydrochloride, 54.75% poly(ethylene oxide) of average  
20 molecular weight 200,000, 25.4% sorbitol, 5% hydroxypropylmethylcellulose  
21 of average molecular weight 11,200, 2% magnesium stearate and 0.05%  
22 butylated hydroxy toluene. The dosage form also contains 132 mg of layer 2,  
23 composed of 53.85% poly(ethylene oxide) of average molecular weight  
24 7,000,000, 40% sodium chloride, 5% hydroxypropylmethylcellulose of  
25 average molecular weight 11,200, 1% red ferric oxide, 0.1% magnesium  
26 stearate and 0.05% butylated hydroxy toluene. The 42 mg semipermeable  
27 laminate is composed of 47.5% cellulose acetate of acetyl content 39.8% and  
28 47.5% cellulose acetate of acetyl content 32.0%, and 5% polyethylene glycol  
29 having an average molecular weight of 3350 is applied to the compressed  
30 bilayer system. A 30 mil (0.76 mm) orifice is drilled on the drug layer side  
31 as the exit orifice. The final system is capable of delivering 14 mg of

1 methylphenidate hydrochloride with an ascending release rate profile  
2 over time.

3 The dosage form delivered methylphenidate hydrochloride in an  
4 ascending rate. The dosage form delivered 0.13 mg in the first hour, 1.16 mg  
5 in the second hour, 1.53 mg in the third hour, 1.61 mg in the fourth hour,  
6 1.75 mg in the fifth hour, 1.79 mg in the sixth hour, 2.13 mg in the seventh  
7 hour, 2.18 mg in the eighth hour, 1.07 mg in the ninth hour, and 0.43 mg in  
8 the tenth hour, 0.17 mg in the eleventh hour, and 0.13 mg in the twelfth hour.

9

10 EXAMPLE 12

11

12 An osmotic dosage form designed, shaped and adapted for delivering  
13 methylphenidate pharmaceutically acceptable salt to a patient in need of  
14 methylphenidate therapy in an ascending release rate profile is manufactured  
15 as follows: First, the procedure used to manufacture the drug layer  
16 granulation in Example 11 is followed in this example. The composition of  
17 the drug layer can comprise from 0% to 30% sorbitol. Next, the following  
18 procedure is used to manufacture the displacement layer:

19 A. Preparation of binder solution.

20 400 g of hydroxypropylmethylcellulose having an average molecular  
21 weight of 11,200 is added to a mixing vessel containing 5000 g of water.  
22 This mixture is stirred until the hydroxypropylmethylcellulose dissolves in  
23 water and a clear solution is formed. This solution is referred to as the binder  
24 solution.

25 B. Preparation of osmotic layer granules.

26 First, 3912 g of hydroxyethylcellulose having an average molecular  
27 weight of 1,300,000 is placed into the bowl of a fluid bed granulator. Next,  
28 400 g of hydroxypropylmethylcellulose having an average molecular weight of  
29 11,200 is added to the bowl. Then, 3,200 g of sodium chloride and 80 g of  
30 black ferric oxide, which have been milled using a 21 mesh screen, is then  
31 placed into the bowl. The bowl is attached to the main body of the granulator

1 and the granulation process is then initiated. Initially, the powder bed inside  
2 the bowl is fluidized for 3 minutes to obtain uniform mixing of the powders.  
3 Next, the binder solution is sprayed at a rate of 80 g/min. During the spraying  
4 process, the process air flow is maintained at 400 cfm and the product  
5 temperature is maintained at 22°C. During the spraying operation, the  
6 solution is sprayed for 30 seconds followed by a shaking time of 10 seconds,  
7 during which time the powders adhering to the filterbags may be dislodged  
8 into the granulating chamber. At the end of the spraying operation,  
9 the granules are dried in the granulating chamber for a additional 10 to  
10 15 minutes to obtain dry granulation. The process parameters may be  
11 adjusted to obtain a quality product. The granules are then passed through  
12 a fluid air mill with a 7 mesh screen for size reduction. The size-reduced  
13 granules are then placed into a blender. Then, 8 g of magnesium stearate  
14 (screened through a 40 mesh screen) and 4 g of powdered butylated hydroxy  
15 toluene (screened through a 60 mesh screen) is added to the granules and  
16 mixed together.

17 C. Compression of the layers.

18 The methylphenidate granules-forming layer and the osmotic granules-  
19 forming layer are compressed together using an automated tablet  
20 compression machine capable of compressing the two layers together  
21 longitudinally. First, 110 mg of methylphenidate granules (layer 1) is added  
22 into the die cavity of a 3/16" diameter tooling, tamped, and then 132 mg of the  
23 osmotic layer granulation (layer 2) is placed into the die and compressed  
24 together using 0.2 metric tons of pressure.

25 D. Application of semipermeable membrane wall.

26 The semipermeable membrane wall forming composition is composed  
27 of 47.5% cellulose acetate 398 (having an acetyl content of 39.8), 47.5%  
28 cellulose acetate 320 (having an acetyl content of 32.0) and 5% polyethylene  
29 glycol having an average molecular weight of 3350. The semipermeable  
30 membrane composition is dissolved in a mixture of methylene chloride and  
31 methanol (the solvents are mixed together in a ratio of 80:20, wt:wt), such that

1 the solids composition of the solution is 4%. The compressed systems are  
2 placed into a 24" coating pan and the coating solution is sprayed onto the  
3 tablets such that the solution is sprayed at a rate of 100 ml/min/gun.  
4 The product temperature is maintained at 35°C. The coating process is  
5 stopped when the desired amount of semipermeable membrane composition  
6 has been sprayed onto the compressed systems.

7 Next, one 30 mil (0.76 mm) orifice is drilled using a laser, on the drug  
8 layer side of the coated systems. The residual solvents remaining after the  
9 coating are removed by drying the systems at 45°C and 45% relative humidity  
10 in an oven for 48 hours. At the end of this drying cycle, the humidity is turned  
11 off and the systems are dried at 45°C for an additional 4 hours to complete  
12 the drying process.

13 A methylphenidate dosage form assembled as described  
14 contains 110 mg of drug containing layer 1, which is composed of 12.8%  
15 methylphenidate hydrochloride, 50.2% to 80.2% poly(ethylene oxide)  
16 of average molecular weight 200,000, 0 to 30% sorbitol,  
17 5% hydroxypropylmethylcellulose of average molecular weight 11,200,  
18 2% magnesium stearate, and 0.05% butylated hydroxy toluene.  
19 The dosage form also contains 132 mg of layer 2, composed of 48.9%  
20 hydroxyethylcellulose of average molecular weight 1,300,000, 40% sodium  
21 chloride, 5% hydroxypropylmethylcellulose of average molecular weight  
22 11,200, 1% red ferric oxide, 0.1% magnesium stearate and 0.05% butylated  
23 hydroxy toluene. 42 mg of a semipermeable laminate composed of 47.5%  
24 cellulose acetate of acetyl content 39.8%, 47.5% cellulose acetate of acetyl  
25 content 32.0%, and 5% polyethylene glycol having an average molecular  
26 weight of 3350 is applied to the compressed bilayer system, and a 30 mil  
27 (0.76 mm) orifice is drilled on the drug layer side as the exit orifice. The final  
28 system is capable of delivering 14 mg of methylphenidate hydrochloride with  
29 an ascending release rate profile over a prolonged period of time.

EXAMPLE 13

The manufacturing procedures described in the above examples are followed, except that in this example a dosage form is provided wherein a drug overcoat and an optional taste-masking coat is overcoated onto the semipermeable walled dosage form. In this example, the drug layer is composed of 14 mg methylphenidate hydrochloride, 27.5 mg sorbitol, 5.5 mg polyvinylpyrrolidone, 61 mg of poly(ethylene oxide) of average molecular weight 2,000,000, 2.2 mg of magnesium stearate and 0.055 mg of butylated hydroxy toluene. The second displacement layer is composed of 72 mg of poly(ethylene oxide) of average molecular weight 7,000,000, 53 mg of sodium chloride, 6.6 mg of polyvinylpyrrolidone, 1.3 mg of ferric oxide, 0.132 mg of magnesium stearate, and 0.066 mg of butylated hydroxy toluene. The semipermeable wall is composed of 20 mg of cellulose acetate of average acetyl content 39.8%, 20 mg of cellulose acetate of average acetyl content 32% and 2 mg of poly(ethylene oxide) of average molecular weight 4000.

The drug-containing overcoat is composed of 60% hydroxypropylmethylcellulose and 40% methylphenidate hydrochloride. The hydroxypropylmethylcellulose is added to water and mixed until a uniform solution results. Then, the methylphenidate hydrochloride is added to this solution and mixed such that a clear solution results. The final solution has a solids composition of 10%. The semipermeable walled dosage forms are placed in a coater and 10 mg of the drug overcoat is sprayed onto the semipermeable wall that surrounds the internal bilayer compressed tablet.

Next, the tablets are dried in the coating pan at 40°C for 10-15 minutes. For the taste masking coat, a suspension of Opadry® is prepared in water such that the solids content is 10%. Opadry® is a powder blend commercially available from Colorcon Inc., and is composed of hydroxypropylmethylcellulose, titanium dioxide, polyethylene glycol and polysorbate 80. The systems coated with the drug containing overcoat are



1 placed into the coater, and the 9 mg of taste-masking coating solution is  
2 sprayed onto the systems. Next, the systems are dried in the coating pan at  
3 40°C for 10-15 minutes to yield the operable dosage forms.

4 The accompanying Figure 3 represents the functionality of the dosage  
5 form of the example. The dosage form releases 4 mg of drug in the first  
6 half hour from the drug overcoat, followed by 0.41 mg in the next half hour,  
7 1.05 mg in the second hour, 1.49 mg in the third hour, 1.57 mg in the fourth  
8 hour, 1.71 mg in the fifth hour, 1.75 mg in the sixth hour, 2.09 mg in the  
9 seventh hour, 2.14 mg in the eighth hour, 1.32 mg in the ninth hour and  
10 0.48 mg in the tenth hour.

#### 11 12 EXAMPLE 14

13  
14 The dosage form is manufactured as described in Example 13,  
15 wherein in the second displacement layer the poly(ethylene oxide) is replaced  
16 with 72 mg of hydroxyethylcellulose of 1,300,000 molecular weight.

#### 17 18 EXAMPLE 15

19  
20 Dosage forms are provided according to the above examples wherein:  
21 (a) the dosage form comprises an overcoat of 8 mg of methylphenidate and  
22 an internal composition comprising 28 mg of methylphenidate; and (b) the  
23 dosage form comprises an overcoat of 12 mg of methylphenidate, and an  
24 internal composition comprising 42 mg of methylphenidate.

#### 25 26 EXAMPLES 16 TO 19

27  
28 Dosage forms are provided by following the above disclosure and  
29 examples to provide dosage forms that deliver a dose of drug, for example,  
30 a central nervous system drug, in an ascending profile in the following  
31 therapeutic ranges: (a) a dosage form that delivers in the first hour 0 to

1 0.308 mg of drug, in the second hour 0.250 mg to 2 mg of drug, in the third  
2 hour 1 mg to 2.4 mg of drug, in the fourth hour 1.1 mg to 2.6 mg of drug, in  
3 the fifth hour 1.23 mg to 2.9 mg of drug, in the sixth hour 1.33 mg to 3.1 mg  
4 of drug, in the seventh hour 1.28 to 2.98 mg of drug, and in the eighth hour  
5 0.76 mg to 1.76 mg of drug; (b) a dosage form exhibiting an ascending dose  
6 profile in the first hour 0 mg to 3.00 mg, in the second hour 2.75 mg to 10 mg,  
7 in the third hour 5 mg to 12 mg, in the fourth hour 5.5 mg to 13 mg, in the fifth  
8 hour 6.15 mg to 14.5 mg, in the sixth hour 6.65 to 15.5 mg, in the seventh  
9 hour 6.4 mg to 14.9 mg, and in the eighth hour 3.8 to 8.8 mg; (c) a dosage  
10 form comprising a drug ascending release rate program of 0 mg to 0.400 mg  
11 in the first hour, 0.376 mg to 1.81 mg in the second hour, 1.29 mg to 2.15 mg  
12 in the third hour, 1.38 mg to 2.3 mg in the fourth hour, 1.54 mg to 2.57 mg in  
13 the fifth hour, 1.66 mg to 2.76 mg in the sixth hour, 1.59 to 2.66 mg in the  
14 seventh hour, and 0.93 to 1.58 mg in the eighth hour; and (d) a dosage form  
15 that delivers an orally administrable drug in an ascending dose of 0 mg to  
16 3.00 mg in the first hour, 2.45 mg to 9.05 mg in the second hour, 6.45 mg to  
17 10.75 mg in the third hour, 6.9 mg to 11.5 mg in the fourth hour, 7.7 mg to  
18 12.9 mg in the fifth hour, 8.3 mg to 13.8 mg in the sixth hour, 7.95 mg to  
19 133 mg in the seventh hour, and 4.65 mg to 7.9 mg in the eighth hour.

20

21

#### EXAMPLES 20 TO 21

22

23 The procedures set forth in the above examples are followed with the  
24 manufacture as described above, except in this invention, a first dosage form  
25 is provided wherein the drug layer comprises 28 mg of methylphenidate  
26 hydrochloride and a second dosage form is provided where the drug layer  
27 comprises 42 mg of methylphenidate hydrochloride.

## DISCLOSURE OF METHOD OF USING THE INVENTION

The invention pertains further to methods for delivering an ascending dose over time to a warm-blooded animal in need of therapy. The invention provides: (a) a method for delivering a dose of drug in an increasing rate to a patient, wherein the method comprises administering orally to the patient a drug in an increasing rate per hour over time, to provide the dose of drug to the patient; (b) a method for delivering a dose of drug in an increasing dose of drug to a patient, wherein the method comprises delivering orally to the patient an orally administrable drug, in an increasing milligram dose per hour over twenty-four hours, to deliver the dose of drug; (c) a method for delivering a drug to a patient from a dosage form over time, wherein the method comprises admitting orally into the patient a dosage form comprising 240 nanograms to 700 milligrams of drug that is delivered in an increasing dose over time; and (d) a method comprising the steps of: (A) admitting into a patient a dosage form comprising: (1) a wall that surrounds a compartment, the wall comprising a semipermeable composition permeable to the passage of fluid, including aqueous-biological fluid of the gastrointestinal tract, and impermeable to the passage of drug; (2) a bilayer in the compartment comprising a first layer comprising a dose of drug, a second layer comprising an osmopolymer, or an osmopolymer and an osmagent, and for imbibing and absorbing fluid for pushing the first layer from the dosage form and thereby providing an increased dose per unit time over time; and (3) at least one exit in the wall communicating with the first layer; (B) imbibing fluid through the semipermeable wall at a rate determined by the permeability of the semipermeable wall and the osmotic gradient across the semipermeable wall causing the second layer to expand and swell; and (C) deliver the drug from the first layer through the exit passageway to provide an ascending, increasing dose of drug to the patient.

1           In summary, it will be appreciated the present invention contributes to  
2   the art an unexpected dosage form that possesses the practical utility for  
3   administering a sustained and increasing dose of drug at a dosage-metered  
4   release rate over time. While the invention has been described and pointed  
5   out in detail with reference to operative embodiments thereof, it will be  
6   understood to those skilled in the art that various changes, modifications,  
7   substitutions and omissions can be made without departing from the spirit of  
8   the invention. It is intended, therefore, that the invention embraces those  
9   equivalents within the scope of the claims.

1 We claim:

2

3 1. An osmotic tablet for administering a dose of drug to a patient,  
4 wherein the osmotic tablet comprises:

5 (a) a drug composition comprising 10 ng to 700 mg of drug;  
6 and

7 (b) an expandable composition comprising 100 ng to 400 mg  
8 of a hydrophilic-expandable polymer; and wherein the drug composition and  
9 the expandable composition are in contacting arrangement, and the osmotic  
10 tablet administers the drug in an ascending-release rate to the patient.

11 2. The osmotic tablet for administering a dose of drug to a patient,  
12 according to claim 1, wherein the drug is a member selected from the group  
13 consisting of an opioid, barbiturate, hypnotic, central nervous system acting  
14 drug, psychostimulant, psychodepressant, cannabinoid and catecholamine.

15 3. The osmotic tablet for administering a dose of drug to a patient  
16 according to claim 1, wherein the drug is a member selected from the group  
17 consisting of amphetamine, dextroamphetamine, methamphetamine,  
18 methylphenidate, racemic methylphenidate, alkylphenidate, ethylphenidate,  
19 threomethylphenidate, phenylisopropylamine, and pemoline.

20 4. The osmotic tablet for administering a dose of drug to a patient  
21 according to claim 1, wherein the drug is a pharmaceutically acceptable salt.

22 5. The osmotic tablet for administering a dose of drug to a patient  
23 according to claim 1, wherein the osmotic tablet imbibes fluid from the patient  
24 and administers the dose of drug.

25 6. An osmotic tablet for administering a dose of drug to a patient,  
26 wherein the osmotic tablet comprises:

27 (a) a drug layer comprising 10 ng to 700 mg of drug; and,

28 (b) a osmotic layer comprising 80% to 95% of a composition  
29 comprising an osmopolymer and an osmagent; and wherein the drug layer  
30 and the osmotic layer comprise a bilayer that administers the drug in an  
31 ascending-release rate to the patient.

1           7.     The osmotic tablet for administering a dose of drug to a patient  
2     according to claim 6, wherein the drug is a member selected from the group  
3     consisting of an opioid, barbiturate, hypnotic, central nervous system acting  
4     drug, psychostimulant, psychodepressant, cannabinoid, and catecholamine.

5           8.     The osmotic tablet for administering a dose of drug to a patient  
6     according to claim 6, wherein the drug comprises a member selected from the  
7     group consisting of amphetamine, dextroamphetamine, methamphetamine,  
8     alkylphenidate, methylphenidate, racemic methylphenidate, ethylphenidate,  
9     threomethylphenidate, phenylisopropylamine, and pemoline.

10          9.     The osmotic tablet for administering a drug to a patient  
11     according to claim 6, wherein the drug is a pharmaceutically acceptable salt  
12     selected from the group consisting of hydrochloride, hydrobromide, fumarate,  
13     phosphate, sulfate, lactate, malate, acetate, tartrate, citrate, pamoate,  
14     maleate, ascorbate, gluconate, aspartate and salicylate.

15          10.    The osmotic tablet for administering a drug to a patient  
16     according to claim 6, wherein the osmotic tablet an oral administration to the  
17     patient imbibes fluid and administers the drug.

18          11.    The osmotic tablet for administering a drug to a patient  
19     according to claim 6, wherein a composition comprising a polymer envelops  
20     the osmotic tablet.

21          12.    The osmotic tablet for administering a drug to a patient  
22     according to claim 6, wherein the osmotic tablet is longer than wide.

23          13.    The osmotic tablet for administering a drug to a patient  
24     according to claim 6, wherein the osmotic tablet is longer than thick.

25          14.    A dosage form comprising:

26               (a)    a first layer comprising 10 ng to 700 mg of drug;

27               (b)    a second layer comprising 80% to 95% of a hydrophilic-  
28     expandable polymer;

29               (c)    a wall comprising a semipermeable composition that  
30     surrounds the first and second layer;

1 (d) an exit in the wall communicating with the first layer for  
2 delivering the drug; and wherein the dosage form when in operation  
3 administers the drug in an ascending rate over time.

4 15. The dosage form according to claim 14, wherein the first layer  
5 comprises a drug selected from the group consisting of an opioid, barbiturate,  
6 hypnotic, central nervous system acting drug, psychostimulant,  
7 psychodepressant, cannabinoid, and catecholamine.

8 16. The dosage form according to claim 14, wherein the first layer  
9 comprises a drug selected from the group consisting of amphetamine,  
10 dextroamphetamine, methamphetamine, methylphenidate, racemic  
11 methylphenidate, alkylphenidate, ethylphenidate, threomethylphenidate,  
12 phenylisopropylamine, and pemoline.

13 17. The dosage form according to claim 14, wherein the dosage  
14 form comprises a length greater than its width and is designed for  
15 administering the drug in an ascending-increasing dose over a sustained  
16 time.

17 18. The dosage form according to claim 14, wherein the dosage  
18 form comprises a length in excess of its width and the second layer  
19 comprises 80% to 95% hydrophilic-expandable polymer that provides for an  
20 ascending-increasing dose of drug over a sustained period.

21 19. The dosage form according to claim 1, wherein the first layer  
22 comprises a poly(alkylene oxide) of 25,000 to 1,000,000 number-average  
23 molecular weight.

24 20. The dosage form according to claim 14, wherein the first layer  
25 comprises a carboxyvinylpolymer of 7,500 to 1,000,000 number-average  
26 molecular weight.

27 21. The dosage form according to claim 14, wherein the first layer  
28 comprises a carboxyalkylcellulose of 10,000 to 700,000 molecular weight.

29 22. The dosage form according to claim 14, wherein the second  
30 layer comprises a poly(alkylene oxide) of 2,500,000 to 10,000,000 number-  
31 average molecular weight.

1           23.    The dosage form according to claim 14, wherein the second  
2 layer comprises a carboxyalkylcellulose of 1,750,000 to 10,000,000 number-  
3 average molecular weight.

4           24.    The dosage form according to claim 14, wherein the first and  
5 second layers comprise a hydroxypropylalkylcellulose.

6           25.    The dosage form according to claim 14, wherein the first and  
7 second layers comprise a hydroxyalkylcellulose.

8           26.    A dosage form comprising:

9               (a)   a first layer comprising 10 ng to 700 mg of drug;

10              (b)   a second layer comprising a composition comprising  
11 80% to 95% of a osmopolymer and an osmagent;

12              (c)   a wall comprising a semipermeable composition that  
13 surrounds the first and second layers;

14              (d)   an exit in the wall communicating with the first layer for  
15 delivering the drug; and wherein the dosage form when in operation  
16 administers the drug in an increasing sustained dose over time.

17           27.    The dosage form according to claim 24, wherein an overcoat  
18 comprising a drug is on the exterior surface of the wall.

19           28.    The dosage form according to claim 24, wherein the first layer  
20 comprises a drug selected from the group consisting of amphetamine,  
21 dextroamphetamine, methamphetamine, methylphenidate, racemic  
22 methylphenidate, alkylphenidate, ethylphenidate, threomethylphenidate,  
23 phenylisopropylamine, and pemoline.

24           29.    The dosage form according to claim 24, wherein the dosage  
25 form comprises a length in excess of its width.

26           30.    The dosage form according to claim 24, wherein the dosage  
27 form comprises a length in excess of its thickness.

28           31.    The dosage form according to claim 24, wherein the second  
29 layer composition comprising the osmopolymer and the osmagent combine  
30 with the dosage form design to deliver the drug in an increasing sustained  
31 dose over time.



1           32.    The dosage form according to claim 24, wherein the first and  
2    second layers comprise a poly(alkylene oxide) and the poly(alkylene oxide) in  
3    the second layer has a higher number-average molecular weight.

4           33.    The dosage form according to claim 24, wherein the first and  
5    second layers comprise a carboxyalkylcellulose and the carboxyalkylcellulose  
6    in the second layer comprises a higher molecular weight.

7           34.    The dosage form according to claim 24, wherein the first and  
8    second layers comprise a hydroxypropylalkylcellulose.

9           35.    The dosage form according to claim 24, wherein the first and  
10   second layers comprise a hydroxyalkylcellulose.  
11   in an increasing dose over time, wherein the method comprises admitting  
12   orally into the patient a dosage form comprising 240 nanograms to 700  
13   milligrams of drug that delivers the drug in an increasing dose per hour over  
14   time to deliver the dose of drug to the patient.



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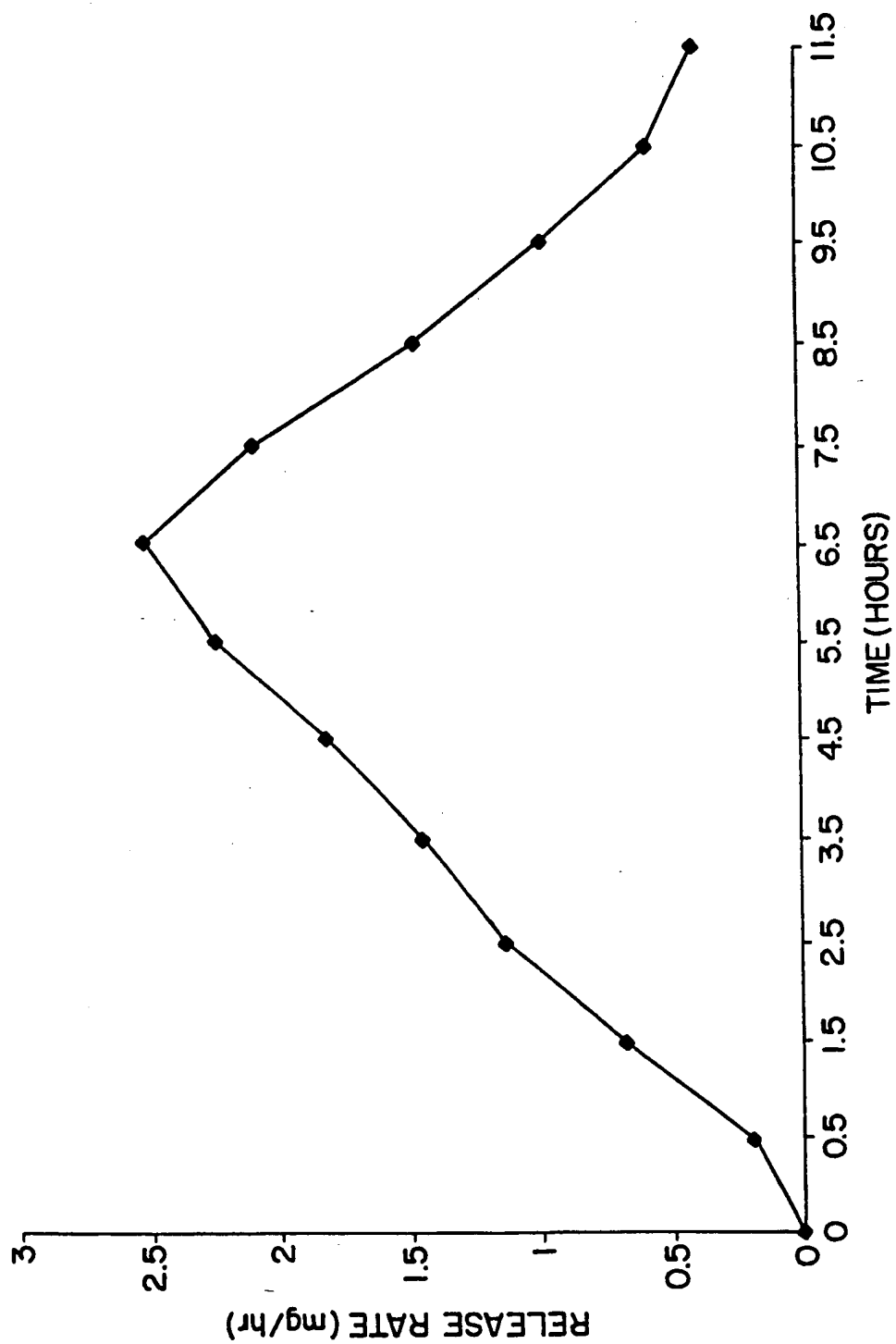


FIG.1

100

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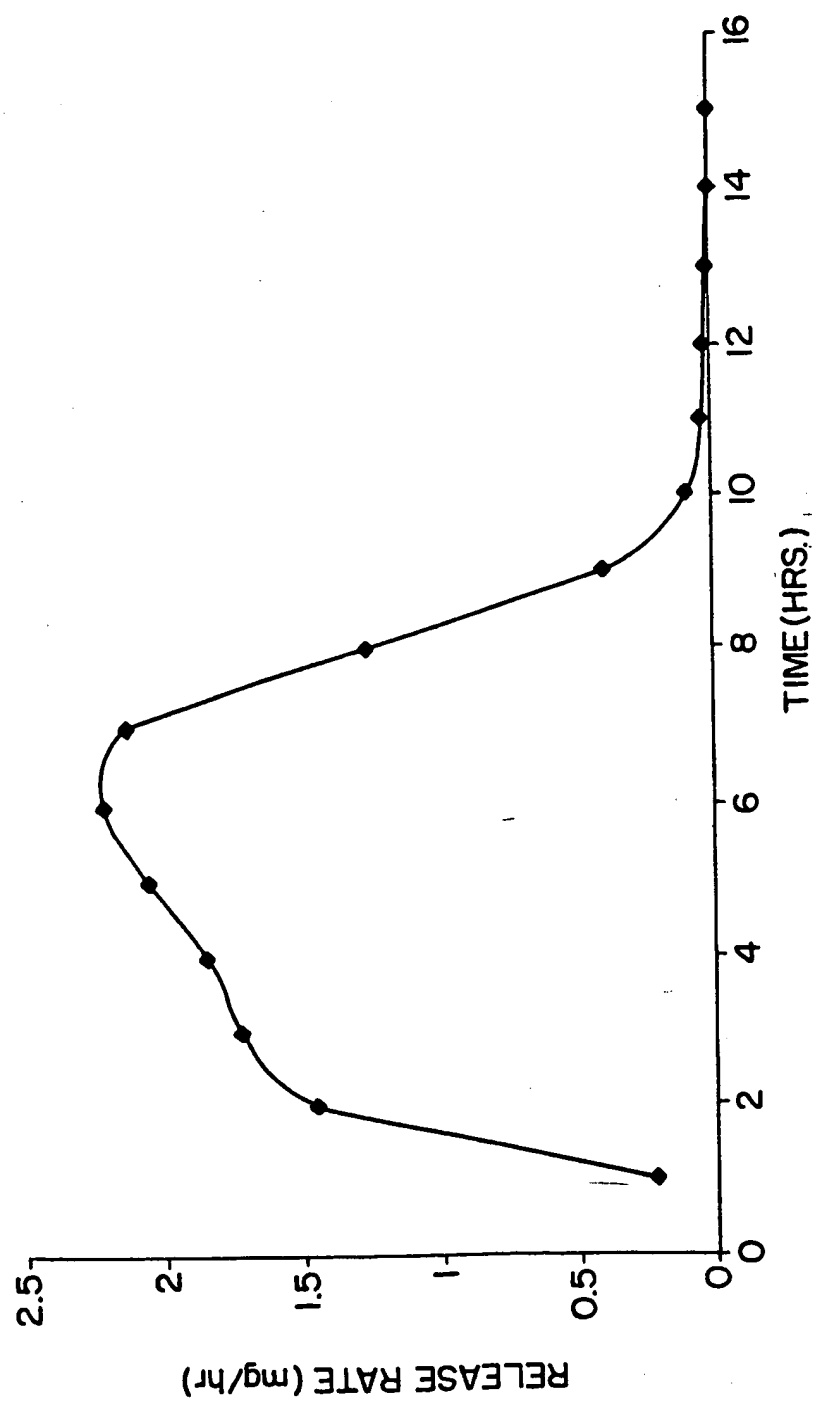
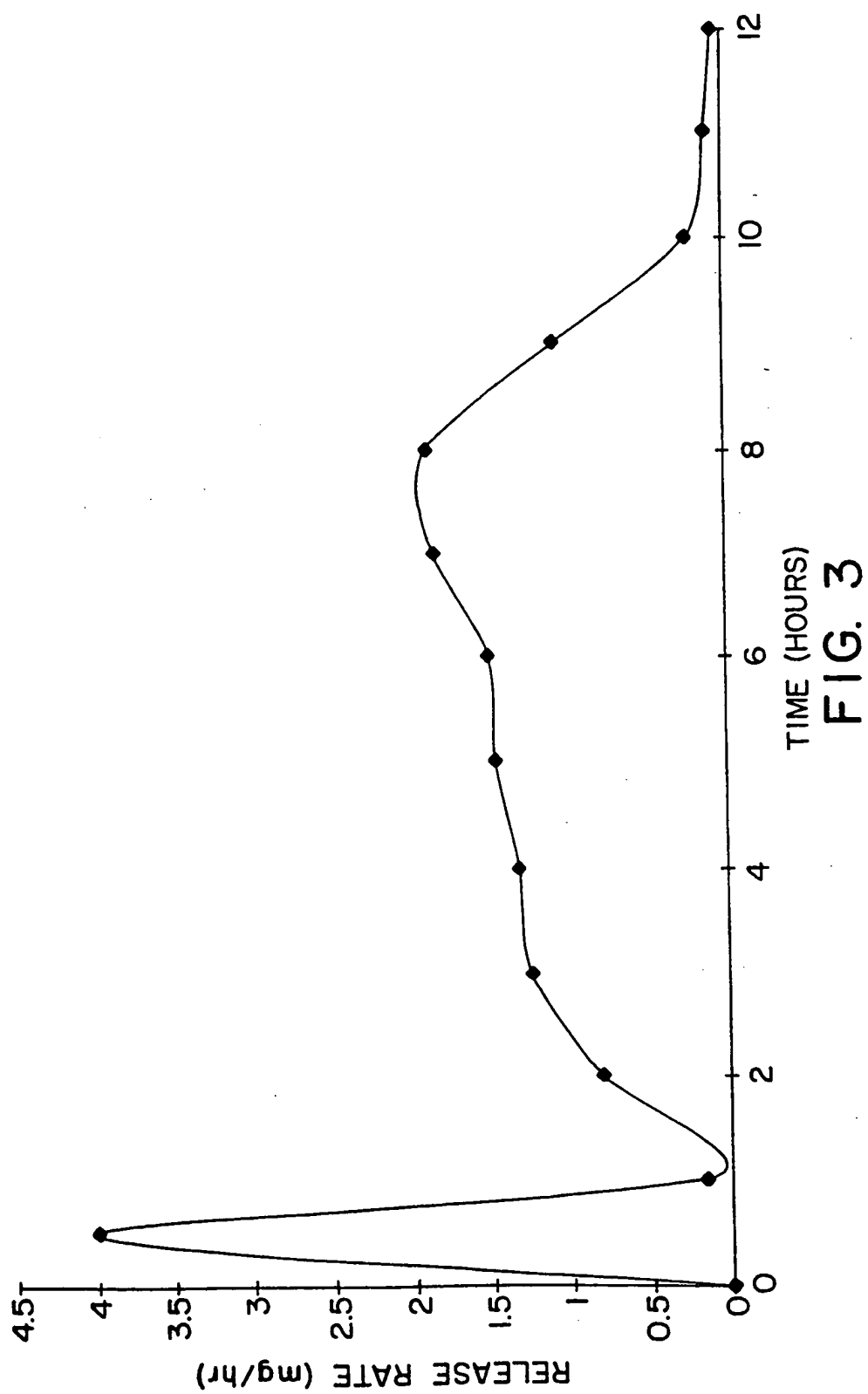


FIG. 2



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# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 97/22016

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 6 A61K9/22		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC 6 A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 91 03247 A (ALZA CORP) 21 March 1991  see page 10 - page 12; example 2 ---	1,5-14, 19,22, 24,26, 31,32,34
X	WO 92 18102 A (ALZA CORP) 29 October 1992  see page 14 - page 17 ---	1,5-11, 14,21, 23,25, 26,31, 33,35
X	WO 95 19174 A (ALZA CORP) 20 July 1995  see page 19 - page 23; example 1 --- -/--	1,4-6, 10-14, 17-19, 22,26
<div style="display: flex; justify-content: space-between;"> <span><input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.</span> <span><input checked="" type="checkbox"/> Patent family members are listed in annex.</span> </div>		
<div style="display: flex;"> <div style="flex: 1;"> <p>* Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="flex: 1;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search  <div style="text-align: center;">23 April 1998</div>		Date of mailing of the international search report  <div style="text-align: center;">06/05/1998</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer  <div style="text-align: center;">Boulois, D</div>

# INTERNATIONAL SEARCH REPORT

International Application No.  
PCT/US 97/22016

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 92 04012 A (ALZA CORP) 19 March 1992</p> <p>see page 15 - page 17; examples 1,2 ---</p>	<p>1,2,4-7, 10,11, 13-15, 19,20, 26,27</p>
X	<p>WO 92 01445 A (ALZA CORP) 6 February 1992</p> <p>see page 19 - page 21; example 1 ---</p>	<p>1,2,5-7, 10-15, 17-20, 22,26</p>
A	<p>US 4 327 725 A (CORTESE RICHARD ET AL) 4 May 1982 see column 14; example 3 -----</p>	<p>1-35</p>